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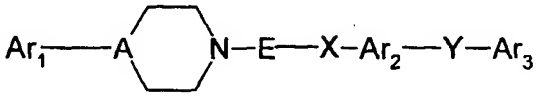
(54) **Title:** ARYL PIPERIDINE DERIVATIVES AS INDUCERS OF LDL-RECEPTOR EXPRESSION



(I)

(57) **Abstract:** The invention concerns a compound of formula (I), wherein Ar_1 represents phenyl, naphthyl or phenyl fused by a C_{3-8}cycloalkyl, where each group is substituted by a group -O-Z and optionally one to three further groups independently represented by R^1; Ar_2 represents phenyl or 5-6 membered heteroaromatic group, where each group is optionally substituted by one to four groups independently selected from halogen, C_{1-4} alkyl and C_{1-4} alkoxy; Ar_3 represents a phenyl or a 5-6 membered heteroaromatic group, where each group is optionally substituted by one to four groups independently selected from hydroxy, alkyl, C_{1-4} alkoxy, C_{2-4} alkenyl, C_{2-4} alkenyloxy, C_{1-4} perfluoroalkoxy, C_{1-4} acylamino or an electron withdrawing group; A represents -C(H)-; E represents -C_{1-6} alkylene-; X represents -CON(H or C_{1-4}alkyl)- or -N(H or C_{1-4}alkyl)CO-;Y represents a direct link, -N(H or C_{1-4}alkyl)CO- or -CON(H or C_{1-4}alkyl)-; Z represents a metabolically labile group; R^1 represents halogen, -S(C_{1-4}alkyl)-, -O-(C_{0-4} alkylene)-R^2 or -(C_{0-4}alkylene)-R^2, where each alkylene group may additionally incorporate an oxygen in the chain, with the proviso that there are at least two carbon atoms between any chain heteroatoms; R^2 represents: i) hydrogen, C_{1-4} perfluoroalkyl, C_{2-3}alkenyl, ii) phenyl, naphthyl, a 5- or 6-membered heteroaromatic group or 1,2,3,4-tetrahydronaphthyl, optionally substituted by one or two halogen, hydroxy, C_{1-4} alkyl, C_{1-4} alkoxy groups, iii) C_{3-8}cycloalkyl, a 3-7 membered heterocycloalkyl, iv) amino, C_{1-4} alkylamino or di-C_{1-4}alkylamino, with the proviso that there are at least two carbon atoms between any chain heteroatoms;and physiologically acceptable salts, solvates and pharmaceutical compositions thereof and their use in treating disorders associated with elevated circulating levels of LDL-cholesterol.

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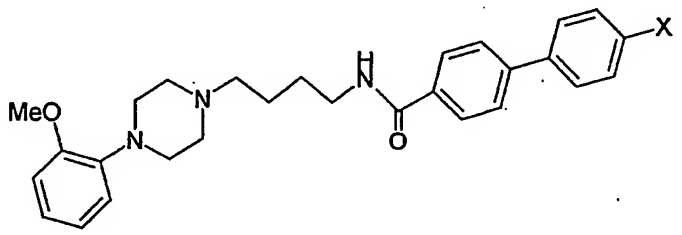
ARYL PIPERIDINE DERIVATIVES AS INDUCERS OF LDL-RECEPTOR EXPRESSION

This invention relates to novel compounds which up-regulate LDL receptor (LDL-r) expression and to processes for their preparation, pharmaceutical compositions containing them and their medical use. More particularly, this invention relates to novel aromatic piperidines and their use in therapy.

Epidemiological studies have clearly demonstrated the correlation between reduction in plasmatic LDL cholesterol and the benefit on cardiovascular events including mortality. LDL cholesterol is eliminated from plasma by specific binding to LDL-r expressed by the liver. Regulation of LDL-r expression occurs in the liver and is mainly dependent on intracellular cholesterol concentration. Increasing free cholesterol concentration leads to a reduced LDL-r expression through a mechanism involving transcriptional factors. Counteracting with this process is expected to up-regulate LDL-r expression in the liver and to increase the clearance of LDL cholesterol.

International Patent Application Number PCT.EP00.06668 concerns the novel use of the SREBP-cleavage activating protein (SCAP) in a screening method, and two compounds are disclosed, namely 4-(4-chloro-benzoylamino)-N-{4-[4-(2-ethoxy-4-ethyl-phenyl)-piperidin-1-yl]-butyl}-benzamide and 4-(4-Benzoyl)-N-{4-[4-(4-isopropyl-2-methoxy-phenyl)-piperidin-1-yl]-butyl}-benzamide hydrochloride, which do not form part of the present invention.

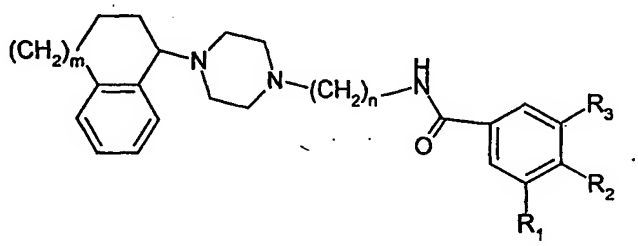
Another publication, Bioorganic and Medicinal Chemistry Letters Vol. 5, 3, 219-222, 1995 discloses compounds having the general formula (A)



A

where X may be COMe, SO_2Me and NH_2, as having high affinity for the dopamine D_3 receptor and postulates their use in CNS disorders, particularly psychiatric illness. The compound of formula A where X is COMe is also disclosed in J.Pharmacol. Exp. Ther. 287; 1 1998 187-197 and Bioorganic and Medicinal Chemistry Letters Vol. 7, 15, 1995-1998, 1997, again as being useful in treating CNS disorders. It will be noted that the examples of the present invention differ from those of formula (A) in use of a piperidine ring rather than a piperazine and in the utility disclosed.

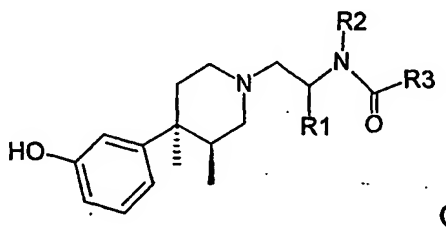
Journal Of Medicinal Chemistry, Vol. 40, 6, 952-960, 1997 discloses compounds of formula (B)



B

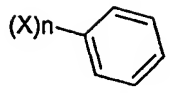
where m=0,1 or 2; n=2 or 3; R_1 and R_3= H or OMe and R^2 may be Ph, as selective 5-HT_{1A} receptor ligands having CNS activity. It will be noted that the examples of the present invention differ from those of formula (B) in use of a piperidine ring rather than a piperazine and in the utility disclosed.

International Patent Application Publication Number WO99/45925 discloses compounds of formula (C)



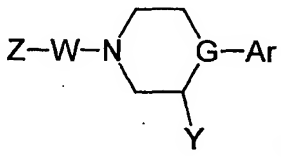
C

where R1 may be hydrogen, R2 may be hydrogen and R3 may be a group



where X may be an aryl group and n may be 1. Specifically disclosed are compounds where the group COR3 is formed from 2- and 4- biphenyl carboxylic acid and R1 and R2 are methyl or hydrogen respectively. The utility of the compounds is as opioid receptor binding agents which may be useful as analgesics. The substitution on the 3- and 4- positions of the piperidine ring leave the compounds of this publication outside the scope of the present invention. Furhtermore, the utility disclosed is different.

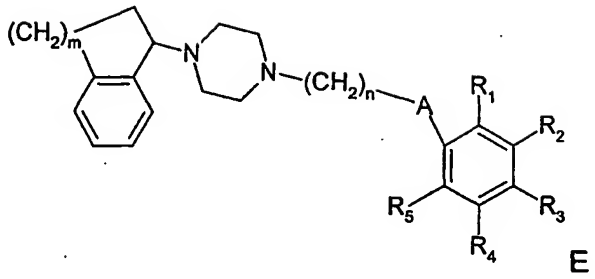
International Patent Application Publication Number WO98/37893 discloses compounds of formula (D)



D

where Ar may represent an optionally substituted phenyl or naphthyl, G may be N or CH_2 (*sic*), W may be an optionally substituted alkylene, Y may be hydrogen and Z may represent a group R_4CONR_5, where R_4 may be an optionally substituted phenyl and R_5 may be hydrogen. These compounds are described as being D2 receptor antagonists useful in the treatment of CNS disorders such as Parkinson's Disease. None of the compounds specifically disclosed fall within the scope of the present invention and the disclosed utlity is different.

International Patent Application Publication Number WO9402473 discloses compounds of formula (E)



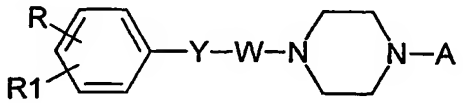
E

where A may be NHCO or CONH; R_1-R_5 may be hydrogen or a benzene ring, m may be 1-3 and n may be 1-3. Specifically disclosed are compounds

No.	A	n	m	R_1	R_2	R_3	R_4	R_5
5	NHCO	2	1	H	H	Ph	H	H
12	NHCO	2	2	H	H	Ph	H	H
19	NHCO	2	3	H	H	Ph	H	H

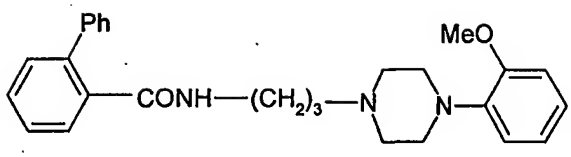
The compounds are described as 5HT-1A agonists having CNS activity and may be used as anti-depressants, anti-hypertensive, analgesics etc. It will be noted that the examples of the present invention differ from those of formula (E) in use of a piperidine ring rather than a piperazine and in the utility disclosed.

International Patent Application Publication Number WO99/45925 discloses compounds of formula (F)



F

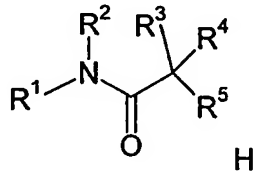
where A may represent a substituted phenyl group, W represents a linear or branched alkylene group having from 2 to 6 carbon atoms; Y may represent a group NHCO or CONH; and R may be a substituted phenyl group. Particularly disclosed is the compound G



(G)

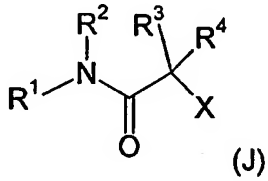
These compounds are described as being α1A-adrenergic receptors useful in the treatment of contractions of the prostate, urethra and lower urinary tract, without affecting blood pressure. It will be noted that the examples of the present invention differ from those of formula (G) in use of a piperidine ring rather than a piperazine and in the utility disclosed.

International Patent Application Publication Number WO98/35957 describes compounds of formula (H)



H

wherein R1-R5 are each individually selected from the group of substituents including hydrogen, halogen, hydroxyl, thiol, lower alkyl, substituted lower alkyl, alkenyl, alkynyl, alkylalkenyl, alkylalkynyl, alkoxy, alkylthio, acyl, aryloxy, amino, amido, carboxyl, aryl, substituted aryl, heterocycle, heteroaryl, substituted heterocycle, heteroalkyl, cycloalkyl, substituted cycloalkyl, alkylcycloalkyl, alkylcycloheteroalkyl, nitro and cyano. Specifically disclosed compounds are those formed by the N-alkylation of a a substituted piperidine or piperazine with a group (J)

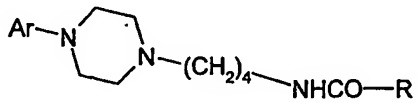


(J)

where X is a leaving group. None of the compounds specifically disclosed fall within the scope of the present invention and the invention is in no way suggested by the disclosure. The compounds are said to be of use as NPY Y5 receptor antagonists in the treatment of obesity, bulemia and related disorders

and NPY Y5 receptor inhibition related disorders such as memory disorders, epilepsy, dyslipidemia and depression. US Patent no. 6,048,900, published after the priority date of the present invention discloses the same information.

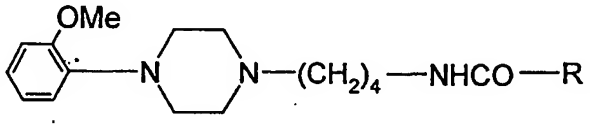
Journal Of Medicinal Chemistry, Vol. 31, 1968-1971, 1988 discloses certain aryl piperazines compounds, which fall outside the present invention, as 5HT-1a Serotonin Ligands as potential CNS agents. Specifically disclosed are compounds of formula (K)



(K)

where Ar=Ph and R = Ph, Ar= 2-OMePh and R =Ph and Ar=2-pyrimidyl and R=Ph.

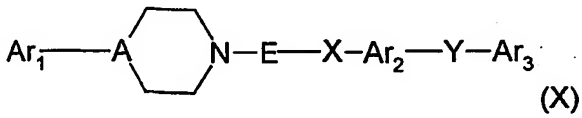
Journal Of Medicinal Chemistry, Vol. 34, 2633-2638, 1991 discloses aryl piperazines having reduced α1 adrenergic affinity. Specifically disclosed is the compound (L)



(L)

where R is 4-(BnO)-phenyl, which falls outside the scope of the present invention.

UK Patent Application Number 0003192.2, which provides background to the disclosure of the present invention, discloses compounds of formula (X)



(X)

wherein

Ar_1 represents a phenyl, naphthyl or phenyl fused by a C_{3-8}cycloalkyl, where each group is optionally substituted by methylenedioxy or one to four groups independently represented by R^1;

Ar_2 represents a phenyl or 5-6 membered heteroaromatic group, optionally substituted by one to four groups independently selected from halogen, C_{1-4} alkyl and C_{1-4} alkoxy;

Ar_3 represents a phenyl or a 5-6 membered heteroaromatic group, optionally substituted by one to four groups independently selected from halogen, hydroxy, nitrile, C_{1-4} alkyl, C_{1-4} alkoxy, C_{2-4} alkenyl, C_{2-4} alkenyloxy, C_{1-4} perfluoroalkyl, C_{1-4} perfluoroalkoxy, C_{1-4} acyl , C_{1-4} alkoxycarbonyl, aminocarbonyl, C_{1-4} alkylaminocarbonyl; di-C_{1-4} alkylaminocarbonyl and C_{1-4} acylamino;

A represents -C(H or C_{1-4} alkyl)- or –N-;

E represents -C_{1-6} alkylene-;

X represents -CON(H or C_{1-4}alkyl)- or –N(H or C_{1-4}alkyl)CO-;

Y represents a direct link, -N(H or C_{1-4}alkyl)CO- or -CON(H or C_{1-4}alkyl)-;

R^1 represents halogen, -O-(C_{0-4} alkylene)-R^2 or –(C_{0-4}alkylene)-R^2, where each alkylene group may additionally incorporate an oxygen in the chain, with the proviso that there are at least two carbon atoms between any chain heteroatoms;

R^2 represents

(i) hydrogen, C_{1-4} perfluoroalkyl,

(ii) phenyl, naphthyl, a 5- or 6-membered heteroaromatic group or 1,2,3,4-tetrahydronaphthyl, optionally substituted by one or two halogen, hydroxy, C_{1-4} alkyl, C_{1-4} alkoxy groups,

(iii) C_{3-8}cycloalkyl, a 3-7 membered heterocycloalkyl,

(iv) amino, C_{1-4} alkylamino or di-C_{1-4}alkylamino, with the proviso that there are at least two carbon atoms between any chain heteroatoms;

or a physiologically acceptable salt, solvate or derivative thereof. Specifically disclosed are the following compounds:

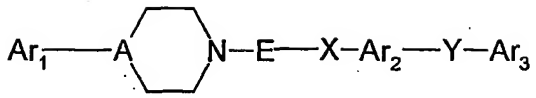
4-(4-chloro-benzoylamino)-N-{4-[4-(5-methyl-2-piperidin-4-yl-phenol)]-butyl}-benzamide;

4-(4-chloro-benzoylamino)-N-{4-[4-(2-ethoxy-4-methyl-phenyl)-piperidin-1-yl]-butyl}-benzamide ;

4'-Trifluoromethyl-biphenyl-4-carboxylic acid {4-[4-(2-ethoxy-4-methyl-phenyl)-piperidin-1-yl]-butyl}-amide;
4'-Trifluoromethyl-biphenyl-4-carboxylic acid (4-{4-[2,5-dimethyl-4-(pyridin-2-ylmethoxy)-phenyl]-piperidin-1-yl}-butyl)-amide;
4-Methyl-2-(4-trifluoromethyl-phenyl)-thiazole-5-carboxylic acid {4-[4-(4-isopropyl-2-methoxy-phenyl)-piperidin-1-yl]-butyl}-amide;
4-(4-chloro-benzoylamino)-N-{4-[4-(2,4-dimethoxy-phenyl)-piperidin-1-yl]-butyl}-benzamide;
4-(4-chloro-benzoylamino)-N-{4-[4-(2,4-diethoxy-phenyl)-piperidin-1-yl]-butyl}-benzamide;
4-(4-chloro-benzoylamino)-N-[4-(4-benzo[1,3]dioxol-5-yl-piperidin-1-yl]-butyl}-benzamide;
4-(4-chloro-benzoylamino)-N-[4-(4-naphthalen-1-yl-piperidin-1-yl]-butyl}-benzamide;
4-(4-chloro-benzoylamino)-N-{4-[4-(5,6,7,8-tetrahydro-naphthalen-2-yl)-piperidin-1-yl]-butyl}-benzamide;
4'-Trifluoromethyl-biphenyl-4-carboxylic acid [4-[4-(2-cyclopropylmethoxy-4-ethyl-phenyl)-piperidin-1-yl]-butyl]-amide;
4'-Chloro-biphenyl-4-carboxylic acid {4-[4-(1-methoxy-naphtalen-2-yl)-piperidin-1-yl]-butyl}-amide;
4-(4-chloro-benzoylamino)-N-{4-[4-(2-trifluoroethoxy-4-methyl-phenyl)-piperidin-1-yl]-butyl}-benzamide;
4-(4-chloro-benzoylamino)-N-{4-[4-(2-methoxy-4-methyl-phenyl)-piperazin-1-yl]-butyl}-benzamide;
or a physiologically acceptable salt, solvate or derivative thereof, all of which are indicative of the range of substitution which may be tolerated on compounds according to the present invention as additionally exemplified by the non-limiting examples disclosed herein.

The present invention concerns pro-drugs of certain compounds related to UK Patent Application Number 0003192.2 and their utility in the field of medicine.

Thus, the present invention provides a compound of formula (I)



(I)

wherein

Ar_1 represents phenyl, naphthyl or phenyl fused by a C_{3-8}cycloalkyl, where each group is substituted by a group -O-Z and optionally one to three further groups independently represented by R^1;

Ar_2 represents phenyl or 5-6 membered heteroaromatic group, where each group is optionally substituted by one to four groups independently selected from halogen, C_{1-4} alkyl and C_{1-4} alkoxy;

Ar_3 represents a phenyl or a 5-6 membered heteroaromatic group, where each group is optionally substituted by one to four groups independently selected from hydroxy, alkyl, C_{1-4} alkoxy, C_{2-4} alkenyl, C_{2-4} alkenyloxy, C_{1-4} perfluoroalkoxy, C_{1-4} acylamino or an electron withdrawing group;

A represents -C(H)- ;

E represents -C_{1-6} alkylene-;

X represents -CON(H or C_{1-4}alkyl)- or –N(H or C_{1-4}alkyl)CO-;

Y represents a direct link, -N(H or C_{1-4}alkyl)CO- or -CON(H or C_{1-4}alkyl)-;

Z represents a metabolically labile group;

R^1 represents halogen, -S(C_{1-4}alkyl), -O-(C_{0-4} alkylene)-R^2 or –(C_{0-4}alkylene)-R^2, where each alkylene group may additionally incorporate an oxygen in the chain, with the proviso that there are at least two carbon atoms between any chain heteroatoms;

R^2 represents

(i) hydrogen, C_{1-4} perfluoroalkyl,C_{2-3}alkenyl,

(ii) phenyl, naphthyl, a 5- or 6-membered heteroaromatic group or 1,2,3,4-tetrahydronaphthyl, optionally substituted by one or two halogen, hydroxy, C_{1-4} alkyl, C_{1-4} alkoxy groups,

(iii) C_{3-8}cycloalkyl, a 3-7 membered heterocycloalkyl,

(iv) amino, C_{1-4} alkylamino or di-C_{1-4}alkylamino, with the proviso that there are at least two carbon atoms between any chain heteroatoms;

or a physiologically acceptable salt or solvate thereof.

Suitable physiologically acceptable salts of the compounds of general formula (I) include acid addition salts formed with pharmaceutically acceptable inorganic acids for example, hydrochlorides, hydrobromides or sulphates, or with pharmaceutically acceptable organic acids for example mesylates, lactates and acetates. More suitably, a physiologically acceptable salt of the compounds of general formula (I) is a mesylate salt.

The solvates may, for example, be hydrates.

References herein after to a compound according to the invention include both compounds of formula (I) and their physiologically acceptable salts together with physiologically acceptable solvates.

Referring to the general formula (I), alkyl, alkylene and alkoxy include both straight and branched chain saturated hydrocarbon groups. Examples of alkyl groups include methyl and ethyl groups, examples of alkylene groups include methylene and ethylene groups, whilst examples of alkoxy groups include methoxy and ethoxy groups.

Referring to the general formula (I), alkenyl includes both straight and branched chain saturated hydrocarbon groups containing one double bond. Examples of alkenyl groups include ethenyl or n-propenyl groups.

Referring to the general formula (I), acyl refers to aliphatic or cyclic hydrocarbons attached to a carbonyl group through which the substituent bonds, such as acetyl.

Referring to the general formula (I), phenyl fused by a C_{3-8}cycloalkyl includes bicyclic rings such as 1,2,3,4-tetrahydronaphthyl, which, for the avoidance of doubt, is linked to the rest of the molecule through the aromatic ring.

Referring to general formula (I), a halogen atom includes fluorine, chlorine, bromine or iodine.

Referring to the general formula (I), C_{1-3}perfluoroalkyl and C_{1-3}perfluoroalkoxy includes compounds which the hydrogens have been partially or fully replaced by fluorines, such as trifluoromethyl and trifluoromethoxy or trifluoroethyl.

Referring to the general formula (I), a 5-6 membered hetroaromatic group includes a single aromatic ring system containing at least one ring heteroatom independently selected from O, N and S. Suitable examples include pyridyl and thiazolyl.

Referring to the general formula (I), reference to a C_{3-8} cycloalkyl group means any single carbocyclic ring system, wherein said ring is fully or partially saturated. Suitable examples include cyclopropyl and cyclohexyl groups.

Referring to the general formula (I), reference to a 3-7 membered heterocycloalkyl group means any single ring system containing at least one ring heteroatom independently selected from O, N and S, wherein said ring is fully or partially saturated.

Suitably, Ar_1 represents a phenyl, naphthyl or 1,2,3,4-tetrahydronaphthyl group, substituted by a group –O-Z, where further optional substitution is effected by R^1. More suitably, Ar_1 represents a substituted phenyl or naphthyl. Preferably Ar_1 represents a substituted phenyl. Equally preferably, Ar_1 represents a substituted naphthyl.

Substitution on Ar_1 is suitably represented by –O-Z and one, two or three further groups independently selected from C_{1-4} alkyl, e.g. methyl, ethyl or iso-propyl, C_{1-4} alkoxy, e.g. methoxy or ethoxy, -O-C_{0-4}alkylene-R^2, e.g. -O-methylene-R^2,

where R^2 represents C_{1-4} perfluoroalkyl, e.g. trifluoromethyl, a 5-6 membered heteroaromatic group, e.g. pyridyl, preferably 2-pyridyl, or a C_{3-8}cycloalkyl, e.g. cyclopropyl.

Substitution on Ar_1 is equally suitably represented by one or two groups independently selected from C_{1-4} alkyl, e.g. methyl or ethyl, C_{1-4} alkoxy, e.g. methoxy, ethoxy, propoxy, isobutoxy, C_{2-3}alkenyloxy, e.g. allyloxy, -O-C_{0-4}alkylene-R^2, e.g. -O-methylene-R^2, where R^2 represents a C_{3-8}cycloalkyl, e.g. cyclopropyl.

Preferably, Ar_1 is a phenyl group substituted by –O-Z and optionally one or two further groups independently selected from methyl, ethyl, isopropyl, methoxy, ethoxy, cyclopropylmethoxy and 2-pyridylmethoxy. Preferably, substitution is in two or three of the 2-, 4- or 5- positions on the phenyl ring.

Equally preferably, Ar_1 is a phenyl or naphthyl group substituted by –O-Z and optionally one further group selected from methyl, ethyl, methoxy, ethoxy, propoxy, isobutoxy, allyloxy and cyclopropylmethoxy. Preferably, where Ar_1 is phenyl, substitution is in one or two of the 2- or 4- positions on the phenyl ring. Preferably, where Ar_1 is naphthyl, the link to group A is through the 1- or 2-position and mono-substitution by R^1 is in either the corresponding 1- or 2-positions.

E is preferably an n-butylene group.

X is suitably a -N(H or C_{1-4} alkyl)CO- group, preferably an -N(H)CO- group.

Y is suitably an -N(H or C_{1-4} alkyl)CO- group or a direct link. Preferably, Y is an -N(H or C_{1-4} alkyl)CO- group. Equally preferably, Y is a direct link.

The group Z is any metabolically labile group which may be cleaved upon administration to a mammal, such as a human, to give the corresponding –OH derivative. For the avoidance of any doubt, compounds of formula (I) have activity in their own right. Such Z groups are clear to those skilled in the art, without undue experimentation, and with reference to the teaching of Burger's

Medicinal Chemistry And Drug Discovery, 5th Edition, Vol 1: Principles And Practice, the principle details relating to prodrugs and metabolites of which is incorporated herein by reference. Suitable Z groups include C_{1-4} acyl, C_{1-4} acyloxymethylene, optionally substituted benzoyl, where optional substitution may be effected by one or more C_{1-4} alkyl, halogen, hydroxy or C_{1-4} alkoxy, -$PO(OR^3)_2$, where R^3 represents hydrogen, C_{1-4} alkyl, phenyl or phenylmethyl, carboxyethylcarbonyl, C_{1-4} alkylaminocarbonyl, C_{1-4} dialkylaminocarbonyl or esters formed with readily available amino acids, e.g. dimethylaminomethylcarbonyl. Z is more sutiably C_{1-4} acyl, e.g. acetyl or -$PO(OR^3)_2$, where R^3 represents hydrogen, C_{1-4} alkyl, phenyl or phenylmethyl, e.g. phosphate.

The group –O-Z is suitably ortho-substituted to the link to the group A.

Where Ar_2 is a 5-6-membered heteroaromatic group, this is suitably a thiazolyl group, optionally substituted by C_{1-4} alkyl, e.g. methyl. Ar_2 is preferably para substituted phenyl.

Suitable electron withdrawing groups on Ar_3 include halogen, nitrile, nitro, C_{1-4}, C_{1-4} perfluoroalkyl, C_{1-4} acyl , C_{1-4} alkoxycarbonyl, aminocarbonyl, C_{1-4} alkylaminocarbonyl; di-C_{1-4} alkylaminocarbonyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylaminosulfonyl and di-C_{1-4} alkylaminosulfonyl, C_{1-4} alkylsulfonyl and C_{1-4}alkylsulfoxy.

Ar_3 is preferably phenyl or a pyridyl group, suitably 2-pyridyl, substituted by a halogen, e.g. chloro or C_{1-4}perfluoroalkyl, e.g. trifluoromethyl.

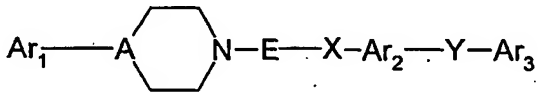
Ar_3 is equally preferably phenyl substituted by a halogen, e.g. chloro, C_{1-4}perfluoroalkyl, e.g. trifluoromethyl, nitrile or C_{1-4}alkylsulfonyl, e.g. methylsulfonyl.

When Ar_3 is phenyl, para- substitution is preferred.

More preferably, Ar_3 is phenyl substituted by a halogen, e.g. chloro or nitrile. Most preferably, Ar_3 is phenyl substituted by a halogen, e.g. chloro.

Particularly preferred compounds of the invention include those in which each variable in Formula (I) is selected from the preferred groups for each variable. Even more preferable compounds of the invention include those where each variable in Formula (I) is selected from the more preferred or most preferred groups for each variable.

A preferred sub-group of a compound of formula (I) is represented by a compound of formula (Ia)



(Ia)

wherein

Ar_1 represents phenyl, naphthyl or phenyl fused by a C_{3-8}cycloalkyl, where each group is substituted by a group -O-Z and optionally one to three further groups independently represented by R^1;

Ar_2 represents a phenyl or 5-6 membered heteroaromatic group, where each group is optionally substituted by one to four groups independently selected from halogen, C_{1-4} alkyl and C_{1-4} alkoxy;

Ar_3 represents a phenyl or a 5-6 membered heteroaromatic group, where each group is optionally substituted by one to four groups independently selected from halogen, hydroxy, nitrile, C_{1-4} alkyl, C_{1-4} alkoxy, C_{2-4} alkenyl, C_{2-4} alkenyloxy, C_{1-4} perfluoroalkyl, C_{1-4} perfluoralkoxy, C_{1-4} acyl , C_{1-4} alkoxycarbonyl, aminocarbonyl, C_{1-4} alkylaminocarbonyl; di-C_{1-4} alkylaminocarbonyl and C_{1-4} acylamino;

A represents -C(H)- ;

E represents -C_{1-6} alkylene-;

X represents -CON(H or C_{1-4}alkyl)- or –N(H or C_{1-4}alkyl)CO-;

Y represents a direct link, -N(H or C_{1-4}alkyl)CO- or -CON(H or C_{1-4}alkyl)-;

Z represents a metabolically labile group;

R^1 represents halogen, -O-(C_{0-4} alkylene)-R^2 or –(C_{0-4}alkylene)-R^2, where each alkylene group may additionally incorporate an oxygen in the chain, with the proviso that there are at least two carbon atoms between any chain heteroatoms;

R^2 represents

(i) hydrogen, C_{1-4} perfluoroalkyl,

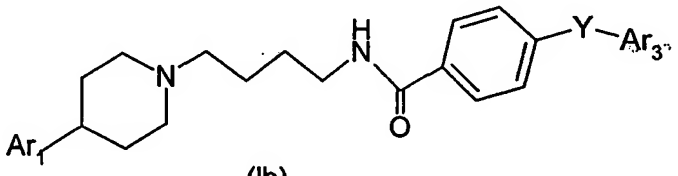
(ii) phenyl, naphthyl, a 5- or 6-membered heteroaromatic group or 1,2,3,4-tetrahydronaphthyl, optionally substituted by one or two halogen, hydroxy, C_{1-4} alkyl, C_{1-4} alkoxy groups,

(iii) C_{3-8}cycloalkyl, a 3-7 membered heterocycloalkyl,

(iv) amino, C_{1-4} alkylamino or di-C_{1-4}alkylamino, with the proviso there are at least two carbon atoms between any chain heteroatoms;

or a physiologically acceptable salt or solvate thereof.

A further preferred sub-group of the present invention is represented by a compound of formula (Ib)



(Ib)

wherein

Ar_1 represents phenyl, naphthyl or 1,2,3,4-tetrahydronaphthyl, where each group is substituted in by a group –O-Z and optionally by one or two further groups independently represented by R^1;

Ar_3 represents phenyl substituted in the para position by a halogen, nitrile or C_{1-4} perfluoroalkyl group;

R^1 represents halogen, C_{1-4} alkyl, C_{1-4} alkyl or –O-(C_{0-4}alkylene)-R^2,

R^2 represents hydrogen, C_{1-4} perfluoroalkyl, a 5- or 6-membered heteroaromatic group or C_{3-8}cycloalkyl;

Y represents a direct link or -N(H)CO-;

Z represents a C_{1-4}acyl group or a $PO(OR^3)_2$, where R^3 represents hydrogen, C_{1-4} alkyl, phenyl or phenylmethyl;

or a physiologically acceptable salt or solvate thereof.

It will be understood that references to compounds of formula (I) hereinbefore and hereinafter apply equally to compounds of formula (Ia) and (Ib).

Suitable compounds according to the invention include:
Acetic acid 2-(1-{4-[4-(4-chloro-benzoylamino)-benzoylamino]-butyl}-piperidin-4-yl)-5-methyl-phenyl ester ;
Phosphoric acid 2-(1-{4-[4-(4-chloro-benzoylamino)-benzoylamino]-butyl}-piperidin-4-yl)-5-methyl-phenyl ester diethyl ester ;
Acetic acid 2-(1-{4-[4-(4-chloro-benzoylamino)-benzoylamino]-butyl}-piperidin-4-yl)-5-ethyl-phenyl ester;
Acetic acid 2-(1-{4-[(4'-cyano-biphenyl-4-carbonyl)-amino]-butyl}-piperidin-4-yl)-5-ethyl-phenyl ester;
Acetic acid 2-(1-{4-[4-(4-chloro-benzoylamino)-benzoylamino]-butyl}-piperidin-4-yl)-5,6,7,8-tetrahydro-naphtalen-1-yl ester ;
Acetic acid 2-(1-{4-[(4'-cyano-biphenyl-4-carbonyl)-amino]-butyl}-piperidin-4-yl)-5,6,7,8-tetrahydro-naphtalen-1-yl ester;
Acetic acid 2-(1-{4-[4-(4-chloro-benzoylamino)-benzoylamino]-butyl}-piperidin-4-yl)-naphtalen-1-yl ester ;
Acetic acid 2-(1-{4-[(4'-cyano-biphenyl-4-carbonyl)-amino]-butyl}-piperidin-4-yl)-naphtalen-1-yl ester;

Phosphoric acid 2-(1-{4-[(4'-cyano-biphenyl-4-carbonyl)-amino]-butyl}-piperidin-4-yl)-5-methyl-phenyl ester diethyl ester;
Phosphoric acid mono-[2-(1-{4-[(4'-cyano-biphenyl-4-carbonyl)-amino]-butyl}-piperidin-4-yl)-5-methyl-phenyl] ester;
Phosphoric acid 2-(1-{4-[(4'-cyano-biphenyl-4-carbonyl)-amino]-butyl}-piperidin-4-yl)-5,6,7,8-tetrahydro-naphtalen-1-yl ester diethyl ester;
Acetic acid 2-(1-{4-[(4'-cyano-biphenyl-4-carbonyl)-amino]-butyl}-piperidin-4-yl)-5-methyl-phenyl ester;
Phosphoric acid 2-(1-{4-[4-(4-chloro-benzoylamino)-benzoylamino]-butyl}-piperidin-4-yl)-5,6,7,8-tetrahydro-naphtalen-1-yl ester diethyl ester;
Phosphoric acid 2-(1-{4-[4-(4-chloro-benzoylamino)-benzoylamino]-butyl}-piperidin-4-yl)-5-ethyl-phenyl ester diethyl ester ;
or a physiologically acceptable salt or solvate thereof.

The compounds of the invention are inductors of LDL-r expression and are thus of use in the treatment of conditions resulting from elevated circulating levels of LDL-cholesterol.

The ability of the compounds of the invention to induce LDL-r expression by human hepatocytes in vitro is determined using a human hepatocarcinoma cell line, Hep G2, as a model system. A reporter gene assay using the LDL-r promotor in front of the reporter gene luciferase is used as a primary screen.

The in vivo profile of the compounds is evaluated by oral administration of the compounds of the invention to fat-fed hamsters. Measurements of VLDL/LDL cholesterol and triglycerides upon treatment allow to determine the activity.

The compounds of the invention are potent and specific inductors of LDL-r expression, which furthermore exhibit good oral bioavailability and duration of action.

Compounds of the invention are of use in the treatment of diseases in which lipid imbalance is important, e.g. atherosclerosis, pancreatitis, non-insulin dependent diabetes mellitus (NIDDM), coronary heart diseases and obesity.

Compounds of the invention are also useful in lowering serum lipid levels, cholesterol and/or triglycerides, and are of use in the treatment of hyperlipemia, hyperlipidemia, hyperlipoproteinemia, hypercholesterolemia and/or hypertriglyceridemia.

The invention therefore provides a compound of formula (I) or a physiologically acceptable salt or solvate thereof for use in therapy, in particular in human medicine.

There is also provided as a further aspect of the invention the use of a compound of formula (I) or a physiologically acceptable salt or solvate thereof in the preparation of a medicament for use in the treatment of conditions resulting from elevated circulating levels of LDL-cholesterol.

In an alternative or further aspect there is provided a method for the treatment of a mammal, including man, in particular in the treatment of conditions resulting from elevated circulating levels of LDL-cholesterol, comprising administration of an effective amount of a compound of formula (I) or a physiologically acceptable salt or solvate thereof.

It will be appreciated that reference to treatment is intended to include prophylaxis as well as the alleviation of established symptoms. Compounds of formula (I) may be administered as the raw chemical but the active ingredient is preferably presented as a pharmaceutical formulation.

Accordingly, the invention also provides a pharmaceutical composition which comprises at least one compound of formula (I) or a physiologically acceptable salt or solvate thereof and formulated for administration by any convenient route. Such compositions are preferably in a form adapted for use in medicine, in particular human medicine, and can conveniently be formulated in a conventional manner using one or more pharmaceutically acceptable carriers or excipients.

Thus compounds of formula (I) may be formulated for oral, buccal, parenteral, transdermal, topical (including ophthalmic and nasal), depot or rectal

administration or in a form suitable for administration by inhalation or insufflation (either through the mouth or nose).

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium starch glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g. sorbitol syrup, cellulose derivatives or hydrogenated edible fats); emulsifying agents (e.g. lecithin or acacia); non-aqueous vehicles (e.g. almond oil, oily esters, ethyl alcohol or fractionated vegetable oils); and preservatives (e.g. methyl or propyl-p-hydroxybenzoates or sorbic acid). The preparations may also contain buffer salts, flavouring, colouring and sweetening agents as appropriate.

Preparations for oral administration may be suitably formulated to give controlled release of the active compound.

For buccal administration the composition may take the form of tablets or lozenges formulated in conventional manner.

For transdermal administration the compounds according to the invention may be formulated as creams, gels, ointments or lotions or as a transdermal patch. Such compositions may for example be formulated with an aqueous or oily base with the addition of suitable thickening, gelling, emulsifying, stabilising, dispersing, suspending, and/or colouring agents.

The compounds of the invention may be formulated for parenteral administration by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form e.g. in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

The compounds of the invention may be formulated for topical administration in the form of ointments, creams, gels, lotions, pessaries, aerosols or drops (e.g. eye, ear or nose drops). Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Ointments for administration to the eye may be manufactured in a sterile manner using sterilised components.

Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilising agents, dispersing agents, suspending agents, thickening agents, or colouring agents. Drops may be formulated with an aqueous or non aqueous base also comprising one or more dispersing agents, stabilising agents, solubilising agents or suspending agents. They may also contain a preservative.

The compounds of the invention may also be formulated in rectal compositions such as suppositories or retention enemas, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

The compounds of the invention may also be formulated as depot preparations. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds of the invention may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

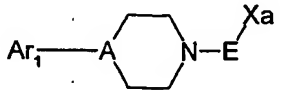
For intranasal administration, the compounds of the invention may be formulated as solutions for administration via a suitable metered or unit dose device or alternatively as a powder mix with a suitable carrier for administration using a suitable delivery device.

The compositions may contain from 0.1% upwards, e.g. 0.1 - 99% of the active material, depending on the method of administration. A proposed dose of the compounds of the invention is 0.25mg/kg to about 125mg/kg bodyweight per day e.g. 20mg/kg to 100mg/kg per day. It will be appreciated that it may be necessary to make routine variations to the dosage, depending on the age and condition of the patient and the precise dosage will be ultimately at the discretion of the attendant physician or veterinarian. The dosage will also depend on the route of administration and the particular compound selected.

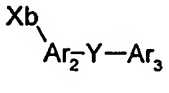
The compounds of formula (I) may, if desired, be administered with one or more therapeutic agents and formulated for administration by any convenient route in a conventional manner. Appropriate doses will be readily appreciated by those skilled in the art. For example, the compounds of formula (I) may be administered in combination with an HMG CoA reductase inhibitor, an agent for inhibition of bile acid transport or fibrates.

A compound of formula (I), or a physiologically acceptable salt, solvate or derivative thereof, may be prepared by the general methods outlined hereafter. In the following description, the groups Ar_1, Ar_2, Ar_3, R^1, R^2, A, E and X are as previously defined for compounds of formula (I), unless specified otherwise.

According to a first general process (A), a compound of formula (I) may be prepared by reaction of a compound of formula (II) with a compound of formula (III)



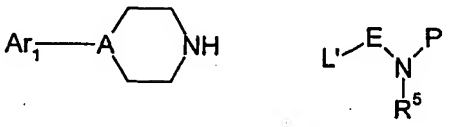
(II)



(III)

where Xa and Xb are suitable reactants to form a group X. For example, where X is N(H or C_{1-4} alkyl)CO, Xa is NH_2 or NH(C_{1-4} alkyl) and Xb is COL where L is OH or a suitable leaving group, such as halide. Such a reaction may be effected under standard amide bond-forming conditions, including those described herein.

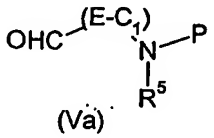
A compound of formula (II) where Xa is NH_2 or NH(C_{1-4} alkyl), may be prepared by reaction of a compound of formula (IV) with a compound of formula (V)



(IV) (V)

where R^5 represents H or C_{1-4}alkyl, L' is a suitable group, such as halide, and P is any suitable N-protecting group, under standard alkylation conditions, including those described herein, followed by removal of the protecting group under standard conditions.

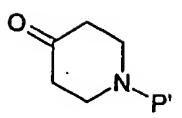
A compound of formula (II) where Xa is NH_2 or NH(C_{1-4} alkyl), may further be prepared by reaction of a compound of formula (IV) with a compound of formula (Va)



(Va)

where R^5 represents H or C_{1-4}alkyl, E-C_1 ('E minus C_1') represents the group E with one less carbon group in its chain and P is any suitable N-protecting group, under standard reductive amination conditions, including those described herein, followed by removal of the protecting group under standard conditions.

A compound of formula (IV), may be prepared by reaction of a compound Ar_1-sal, where sal represents the lithium or magnesium ion of Ar_1, with a compound of formula (VI)

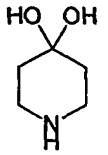


(VI)

where P' represents a suitable N-protecting group, such as acetyl, benzyl or benzyl-4-oxo-1 carboxylate, followed by the steps of dehydration, reduction of the resulting double bond, and finally, removal of the protecting group P'. Such chemistry has been described, for example, in European Patent Appliction no. 0630887.

Alternatively, a compound of formula (IV) where Ar_1 is substituted by an activated ortho or para activating group for the reaction centre, Act, e.g. methoxy or hydroxy, may be prepared by reaction of a compound of formula Ar_1-Act, with a compound of formula (VI) under suitable reaction conditions such as e.g. trifluoroborane or acetic acid and aqueous hydrochloric acid, to form a tetrahydropyridyl ring, followed by reduction, e.g. under hydrogenation conditions, of the resulting double bond and finally deprotection of the N-protecting group, P' under standard conditions.

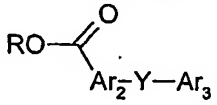
Alternatively, a compound of formula (IV) where where Ar_1 is substituted by an activated ortho or para activating group for the reaction centre, Act, e.g. methoxy or hydroxy may be prepared by reaction of a compound of formula Ar_1-Act, with a compound of formula (VII)



(VII)

under suitable reaction conditions such as e.g. acetic acid and aqueous hydrochloric acid to form a tetrahydropyridyl ring, followed by suitable N-protection, then reduction, e.g. under hydrogenation conditions, of the resulting double bond and finally deprotection of the N-protecting group.

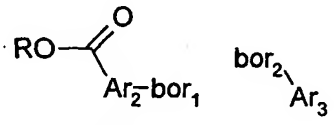
A compound of formula (III) may be prepared by standard methods including, where Xb is CO_2H, deprotection of a compound of formula (X)



(X)

where R is a suitable carboxylic acid protecting group, such as methyl.

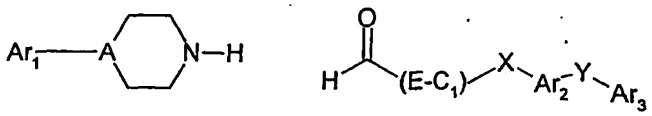
A compound of formula (X) where R is OH or a suitable protecting group and Y is a direct link, may be prepared by reaction of a compound of formula (XI), with a compound of formula (XII)



(XI) (XII)

where bor_1 represents a boronic acid group or a halide, e.g. bromide or iodide, and bor_2 represents a suitable boronic acid group or a halide, e.g. bromide or iodide for coupling, under conditions suitable for boronic acid coupling, e.g. using palladium (0) and sodium carbonate.

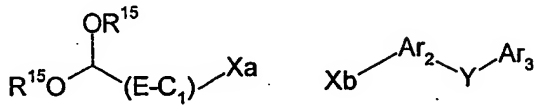
According to a second general process (B), a compound of formula (I) may be prepared by reaction of a compound of formula (IV) with a compound of formula (XIII)



(IV) (XIII)

where E-C_1 ('E minus C_1') means that the chain length of group E is one carbon less than that in the resulting compound (I), under standard reductive amination conditions, e.g. sodium triacetoxyborohydride and acetic acid in a suitable solvent, such as dichloromethane.

A compound of formula (XIII) may be prepared by reaction of a compound of formula (XIV) with a compound of formula (XV)



(XIV) (XV)

where R^{15} is a suitable alkyl protecting group for oxygen, such as methyl, and Xa and Xb are suitable reactants to form a group X, as defined hereinbefore, followed by removal of the protecting group, under acidic conditions.

According to a third general process (C), a compound of formula (I) may be prepared by reaction of a different compound of formula (I), by well known methods. For example a compound of formula (I) where Ar_1 is substituted by C_{1-4} alkoxy may be prepared from the corresponding compound of formula (I) where the substituent is hydroxy by standard O-alkylation methods.

Compounds of formula (V), (VI), (VII), (VIII), (IX), (XI), (XIV) and (XV), are known or may be prepared by standard methods, e.g. as substantially described herein.

The protecting groups used in the preparation of compounds of formula (I) may be used in conventional manner. See for example 'Protective Groups in Organic Chemistry' Ed. J. F. W. McOmie (Plenum Press 1973) or 'Protective Groups in Organic Synthesis' by Theodora W Greene and P M G Wuts (John Wiley and Sons 1991).

Conventional amino protecting groups may include for example aralkyl groups, such as benzyl, diphenylmethyl or triphenylmethyl groups; and acyl groups such as N-benzyloxycarbonyl or t-butoxycarbonyl.

Conventional carboxylic acid protecting groups include methyl and ethyl groups.

The invention is further described with reference to the following non-limiting examples.

Abbreviations :

THF- Tetrahydrofuran, BF_3-Et_2O- Boron trifluoride diethyl etherate, DCM-Dichloromethane, TEA- triethylamine, EtOH- Ethanol, EtOAc- Ethyl acetate, IPr_2O- Di-isopropyl ether, TFA- Trifluoroacetic acid, Pd/C- Palladium on carbon, Et_2O- diethyl ether, IPrOH- Isopropanol, $IprNH_2$- Isopropylamine, NH4OH-Ammoniaque, Chex- cyclohexane, MeOH- Methanol, DMF- Dimethyl formamide, EDCI- 1-(3-dimethylaminopropyl)-, ethylcarbodiimide hydrochloride, HOBt- 1-Hydroxybenzotriazole, MeCN- Acetonitrile, rt- Room temperature, CDI-Carbonyle diimidazole, nBuOH- nButanol, AcOH- Acetic acid CH_3SO_3H- Methane sulfonic acid, $MgSO_4$- Magnesium sulfate, Na_2SO_4- Sodium sulfate, HATU- O-(7-Azabenzotriazol-1-yl)-N,N,N'N'-hetramethyluroniumhexafluorophosphate

Intermediate 1

4-(4-Chloro-benzoylamino)-benzoic acid ethyl ester

A solution of 4-Amino-benzoic acid ethyl ester (124.0 g, 0.75 mol) in THF/DCM (500 mL/1000 mL) was treated with TEA (120 mL, 1.15 eq.) and 4-Dimethylaminopyridine (1.3 g, catalytic amount). At -7 °C a solution of 4-Chloro-benzoyl chloride (152 g, 1.15 eq.) in THF (100 mL) was added dropwise. The resulting mixture was stirred mechanically for 48 hours. The solvent was evaporated off and the residue was taken up in EtOAc/DCM (30/70). A concentrated NaOH solution was added until pH = 12. A white solid precipated out and was collected (156.8 g, 0.52 mol). The organic layer was dried over Na_2SO_4. The solvent was evaporated off and crystallization from iPr_2O gave a second batch of the title compound (63.2 g, 0.21 mol).

^1H NMR ($CDCl_3$, 250 MHz) δ 8.1 (s, 1 H), 7.9 (d, 2H), 7.7 (d, 2H), 7.6 (d, 2H), 7.3 (d, 2H), 4.3 (q, 2H), 1.3 (t, 3H).

Intermediate 2

4-(4-Chloro-benzoylamino)-benzoic acid

A suspension of intermediate 1 (220 g, 0.72 mol) in 2000 mL of EtOH was treated with a 1N NaOH solution (1000 mL). The resulting suspension was

heated at reflux overnight. A white solid precipated out. At reflux, concentrated HCl solution was added until pH = 1. Under rigorous mechanical stirring, the resulting suspension was cooled down. A white solid was collected and dried under reduced pressure to give the title compound in a quantitative yield.
^{1}H NMR (DMSO, 250 MHz) δ 10.5 (s, 1 H), 7.9 (d, 2H), 7.8 (s, 4H), 7.5 (d, 2H).
Ref : J. Pharm. Sci. (1979), 68(3), 332-5

Intermediate 3
4-(4-chloro-benzoylamino)-N-[4-(4,4-diethoxy-butyl)]-benzamide
To a solution of intermediate 2 (10.0 g, 36.3 mmol) in DMF (60 mL), was added 4-Aminobutyraldehyde diethyl acetal (6.44 g, 1.1 eq.), HOBt (7.35 g, 1.5 eq.), CDI (8.8 g, 1.5 eq.) and TEA (7.5 mL, 1.5 eq.). The reaction was stirred at rt for 24 hours. A precipitate was formed. Water (50 mL) was added and the reaction was filtered off. The precipitate was washed with H_2O and dried to give the title compound (11.0 g, 26 mmol) as a white solid.
^{1}H NMR (DMSO, 250 MHz) δ 10.6 (s, 1H), 8.45 (t, 1H), 8.1 (d, 2H), 7.9 (s, 4H), 7.7 (d, 2H), 4.55 (m, 1H), 3.7-3.3 (m, 6H), 1.7 (m, 4H), 1.15 (t, 6H).

Intermediate 4
4-(4-chloro-benzoylamino)-N-[4-(4-oxo-butyl)]-benzamide
To a suspension of intermediate 3 (11.0 g, 26 mmol) in acetone (100 mL) was added a 1N HCl solution (50 mL). The reaction was stirred at reflux for 2 hours. The solvent was evaporated off and the aqueous phase was treated with a saturated $NaHCO_3$ solution until PH = 9-11. The precipitate was filtered off, washed with H_2O and dried to give the title compound (8.3 g, 24 mmol) as a white powder.
MP : 220°C

Intermediate 5
2-(1-Benzyl-1,2,3,6-tetrahydro-pyridin-4-yl)-5-methyl-phenol
To a solution of m-Cresol (20.0 g, 0.185 mol) and 1-Benzyl-4-piperidone (35.0 g, 1.0 eq.) was added dropwise BF_3-Et_2O (71 mL, 3.0 eq). The mixture was stirred at 100°C for 24 hours. After cooling to rt, the mixture was treated with a 1N HCl solution (400 mL). The resulting solution was extracted with DCM. The organic layer was dried over Na_2SO_4 and evaporated to dryness to give an oil which was

crytallized in cyclohexane to give the title compound (40.0 g, 0.14 mol) as a yellow powder.
GC/MS :M+ $C_{19}H_{21}NO$ 279

Intermediate 6
5-Methyl-2-piperidin-4-yl-phenol
To a solution of intermediate 5 (40.0 g, 0.14 mol) in EtOH (600 mL) and THF (50 mL) was added Pd/C,10% (4 g) and the reaction was stirred under an atmospheric pressure of hydrogen at 50°C for 56 hours. The reaction mixture was filtered through a bed of celite. The filtrate was evaporated under reduced pressure to give the title compound as a white powder in a quantitative yield.
GC/MS: M+ $C_{12}H_{17}NO$ 191

Intermediate 7
2-(1-Benzyl-1,2,3,6-tetrahydro-pyridin-4-yl)-5-ethyl-phenol
A solution of 3-Ethyl-phenol (6.1 g, 0.05 mol) and 1-Benzyl-4-piperidone (10.0 g 1.05 eq.) in acetic acid (100 mL) was treated with HCl gaz for 10 min. The mixture was stirred at 95°C for 30 min. After cooling to rt, the mixture was treated again with HCl gaz for 5min. The resulting solution was allowed to stir at rt for 4 days. The solvent was evaporated under reduced pressure and the residue was diluted with H_2O and extracted with DCM. The organic layer was washed with a 2N NaOH solution, H_2O and brine, dried over Na_2SO_4 and evaporated to dryness. The residue was flash chromatographed using MeOH/DCM (5/95) to give the title compound (8.0 g, 0.027 mol) as a yellow oil in 54% yield.
GC/MS: M+ $C_{20}H_{23}NO$ 293

Intermediate 8
5-Ethyl-2-piperidin-4-yl-phenol
To a solution of intermediate 7 (8.0 g, 0.027 mol) in EtOH (100 mL) was added Pd/C,10% (0.8 g) and the reaction was stirred under an atmospheric pressure of hydrogen for 24 hours. The reaction mixture was filtered through a bed of celite. The filtrate was evaporated under reduced pressure to give the title compound (4.9 g, 0.024 mol) as a yellow oil in a 88% yield.
GC/MS: M+ $C_{13}H_{19}NO$ 205

Intermediate 9

1-Benzyl-4-[2-(tert-butyl-dimethyl-silanyloxy)-4-ethyl-phenyl]-1,2,3,6-tetrahydro-pyridine

To a solution of intermediate 7 (3.0 g, 0.01 mol) in DMF (20 mL) was added at 50°C NaH (1.1 eq.) (60% in oil dispersion). The reaction was stirred for 15 min and the terbutyl dimethyl silyl chloride (1.65 g, 0.011 mol) was added and the reaction was stirred for 18 hours at rt.

The reaction was concentrated in vacuo and the residue was diluted with DCM, washed with water, dried over Na_2SO_4 and evaporated off. The title compound was obtained (3.1 g, 7.6 mmol) as a yellow oil in a 77% yield.

GC/MS: M+ $C_{26}H_{37}NOSi$ 407

Intermediate 10

4-[2-(tert-Butyl-dimethyl-silanyloxy)-4-ethyl-phenyl]-piperidine

The same method was employed as in the preparation of intermediate 8 but starting from intermediate 9 gave the title compound as an oil in a 83%.

GC/MS: M+ $C_{19}H_{33}NOSi$ 319

Intermediate 11

2-(4-{4-[2-(tert-Butyl-dimethyl-silanyloxy)-4-ethyl-phenyl]-piperidin-1-yl}-butyl)-isoindole-1,3-dione

A solution of intermediate 10 (2.0 g, 6.2 mmol) in acetone (800 mL) was treated with K_2CO_3 (1.7 g, 2.0 eq.) and *N*-(4-Bromobutyl)-phtalimide (2.1 g, 1.2 eq.). The resulting mixture was stirred under reflux for 6 hours. After cooling to rt the reaction mixture was filtered off. The cake was washed with acetone. The filtrate was evaporated off to give after flash chromatography using (DCM/MeOH, 95/5) as eluent the title compound (2.1 g, 4 mmol) as yellow crystals in a 66% yield.

GC/MS: M+ $C_{31}H_{44}N_2O_3Si$ 520

Intermediate 12

4-{4-[2-(tert-Butyl-dimethyl-silanyloxy)-4-ethyl-phenyl]-piperidin-1-yl}-butylamine

A solution of intermediate 11 (2.1 g, 4 mmol) in MeOH (50 mL) was treated with hydrazine hydrate (0.23 mL, 1.2 eq.). The resulting mixture was stirred at 60 °C

for 5 hours. After evaporation under reduced pressure the residue was taken up in water and treated with a concentrated HCl solution until PH = 4. The white precipitate was filtered off, washed with water and the filtrate was treated with a concentrated NaOH solution until PH = 13. Extraction with DCM, drying over Na_2SO_4 and filtration gave the title compound (0.7 g, 1.8 mmol) as a yellow oil in a 45% yield.
GC/MS: M+ $C_{23}H_{42}N_2OSi$ 390

Intermediate 13
4'-Cyano-biphenyl-4-carboxylic acid (4-{4-[2-(tert-butyl-dimethyl-silanyloxy)-4-ethyl-phenyl -piperidin-1-yl}-butyl)-amide
To a solution of intermediate 12 (0.7 g, 1.8 mmol) in dry DCM (25 mL) was added the available 4'-Cyano-biphenyl-4-carboxylic acid (0.36 g, 0.9 eq.), EDCI (0.68 g, 2.0 eq.), HOBt (0.48 g, 2.0 eq.) and TEA (0.5 mL, 2.0 eq.). The resulting mixture was stirred for 5 hours at rt. The residue was washed with water and brine. The organic layer was dried over Na_2SO_4 and evaporated off. Purification by flash chromatography using DCM/MeOH, 90/10 as eluent gave the title compound (0.7 g, 1.17 mmol) as white crystals in a 73% yield.
MP: 140°C
LC/MS: $[M+H^+]$ 596 $C_{37}H_{49}N_3O_2Si$

Intermediate 14
1-[4-(1-Hydroxy-5,6,7,8-tetrahydro-naphtalen-2-yl)-3,6-dihydro-2H-pyridin-1-yl]-ethanone
The same method was employed as in the preparation of intermediate 5 but starting from the 5,6,7,8-tetrahydro-1-naphtol and N-Acetyl-piperidone to give the title compound as a powder after crystallization in CH_3CN in a 100% yield.
GC/MS: M+ $C_{17}H_{21}NO_2$ 271

Intermediate 15
1-[4-(1-Hydroxy-5,6,7,8-tetrahydro-naphtalen-2-yl)-piperidin-1-yl]-ethanone
To a solution of intermediate 14 (55.0 g, 0.203 mol) in AcOH (500 mL) was added Pd/C,10% (2 g) and the reaction was stirred under an atmospheric pressure of hydrogen at 50°C for 24 hours. The mixture was filtered through a

bed of celite. The filtrate was evaporated under reduced pressure to give the title compound (55.0 g, 0.201 mol) as a yellow powder.
GC/MS: M+ $C_{17}H_{22}NO_2$ 273

Intermediate 16
2-Piperidin-4-yl-5,6,7,8-tetrahydro-naphtalen-1-ol
To a solution of intermediate 15 (27.0 g, 0.099 mol) in EtOH (750 mL) was added a solution of NaOH (250 mL) in H_2O (250 mL). The reaction was stirred under reflux for 16 hours. After cooling, the reaction was concentrated under reduced pressure, was diluted with DCM and washed with water. The organic layer was dried over Na_2SO_4 and evaporated to dryness to give after flash chromatography using DCM/MeOH/NH4OH 30,30,30 as eluent, the title compound (9.7 g, 0.042 mol) as a pink gummy oil in a 42.5% yield.
^1H NMR ($CDCl_3$, 300 MHz) δ 7.9 (bs, 1H), 6.8 (d, 1H), 6.6 (d, 1H), 3.4 (m, 2H), 3.1 (m, 2H), 2.8 (m, 4H), 1.8-1.4 (m, 10H).

Intermediate 17
2-(4,4-Diethoxy-butyl)-isoindole-1,3-dione
To a solution of Isobenzofuran-1,3-dione (10.0 g, 0.068 mol) in toluene (200 mL) were added 4-Aminobutyraldehyde diethyl acetal (14.5 g, 1.2 eq.) and TEA (14.0 mL, 1.5 eq.). The reaction was stirred to reflux for 16 hours. The toluene was removed under vacuo and the residue was dissolved in Et_2O and washed with water. The organic phase was dried over Na_2SO_4 and concentrated under vacuo to give the title compound (21.0 g, 1.0 eq.) as an oil in a quantitative yield.
GC/MS: M+ $C_{16}H_{21}NO_4$ 291

Intermediate 18
4-(1,3-Dioxo-1,3-dihydro-isoindole-2-yl)-butyraldehyde
To a solution of intermediate 17 (21.0 g, 0.068 mol) in acetone (200 mL) was added a 1N HCl solution (100 mL) and the reaction was stirred to reflux for 2 hours. The solvent was then evaporated and a 1N NaOH solution (200 mL) was added. The product was extracted with DCM and the organic phase was dried over Na_2SO_4 and concentrated under vacuo. The title compound was obtained as a yellow oil (8.4 g, 0.039 mol) in a 59% yield.

^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.6 (s, 1H), 7.8 (m, 2H), 7.4 (m, 2H), 3.6 (t, 2H), 2.4 (t, 2H), 1.8 (m, 2H).
Ref: J. Med. Chem. (1992), 35, 3239-46.

Intermediate 19
2-{4-[4-(1-Hydroxy-5,6,7,8-tetrahydro-naphtalen-2-yl)-piperidin-1-yl]-butyl}-isoindole-1,3-dione
The same method was employed as in the preparation of example 1 but starting from the intermediates 16 and 18 to give after flash chromatography using (DCM/MeOH, 90/10 and 1% ammoniac solution) as eluent, the title compound as a gummy oil in a 46% yield.
^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.9 (m, 2H), 7.75 (m, 2H), 6.9 (d, 1H), 6.8 (d, 1H), 6.4 (bs, 1H), 3.85 (m, 2H), 3.5 (m, 2H), 3.0 (m, 1H), 2.9 (m, 2H), 2.8 (m, 2H), 2.5 (m, 4H), 2.1 (m, 2H), 1.87 (m, 10H).

Intermediate 20
2-[1-(4-Amino-butyl)-piperidin-4-yl]-5,6,7,8-tetrahydro-naphtalen-1-ol
The same method was employed as in the preparation of intermediate 12 but starting from intermediate 19 to give the title compound as a red oil in a 90% yield.
^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.0 (d, 1H), 6.6 (d, 1H), 3.1 (m, 2H), 2.9 (m, 1H), 2.65 (m, 4H), 2.6 (m, 2H), 2.45 (m, 2H), 2.1 (m, 2H), 1.85 (m, 8H), 1.5 (m, 6H).

Intermediate 21
1-[4-(1-Hydroxy-naphtalen-2-yl)-3,6-dihydro-2H-pyridin-1-yl]-ethanone
The same method was employed as in the preparation of intermediate 14 but starting from the 1-Naphtol gave the title compound as a white solid in a 54% yield.
GC/MS: M+ $C_{17}H_{17}NO_2$ 267

Intermediate 22
1-[4-(1-Hydroxy-naphtalen-2-yl)-piperidin-1-yl]-ethanone
A solution of intermediate 21 (29.0 g, 0.112 mol) in a mixture of cyclohexene (450 mL), MeOH (100 mL), THF (350 mL) was treated with $Pd(OH)_2$, 50% (14 g). The resulting solution was allowed to stir at reflux for 4 days . After cooling,

the reaction mixture was filtered through a bed of celite. The filtrate was evaporated to dryness to give the title compound as a white solid (22.0 g, 0.082mol) in a 73% yield after recrystallization from CH_3CN.
LC/MS: [M+H+] $C_{17}H_{19}NO_2$ 270

Intermediate 23
2-Piperidin-4-yl-naphtalen-1-ol
The same method was employed as in the preparation of intermediate 16 but starting from the intermediate 22 gave the title compound as a brown solid in a quantitative yield.
^{1}H NMR (DMSO, d^6, 300 MHz) δ 9.3 (s, 1H), 8.25 (dd, 1H), 7.8 (dd, 1H), 7.5 (m, 3H), 7.25 (m, 1H), 3.45 (m, 3H), 3.1 (m, 2H), 2.9 (m, 4H).

Intermediate 24
2-{4-[4-(1-Hydroxy-naphtalen-2-yl)-piperidin-1-yl]-butyl}-isoindole-1,3-dione
The same method was employed as in the preparation of intermediate 19 but starting from the intermediate 23 gave the title compound as a pink solid in a 61% yield.
^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.3 (dd, 2H), 7.95 (m, 2H), 7.8 (m, 3H), 7.6-7.2 (m, 4H), 3.85 (m, 2H), 3.25 (m, 2H), 2.85 (m, 2H), 2.55 (m, 2H), 2.35 (m, 2H), 1.95 (m, 2H), 1.8 (m, 4H).

Intermediate 25
2-[1-(4-Amino-butyl)-piperidin-4-yl]-naphtalen-1-ol
The same method was employed as in the preparation of intermediate 12 but starting from intermediate 24 to give the title compound as a yellow solid in a 79% yield.
LC/MS(ES): M+ $C_{19}H_{26}N_2O$ 298

Intermediate 26
4'-Acetyl-biphenyl-4-carboxylic acid ethyl ester
To a solution of 16 g (0.058 mol.) of 4-iodo-benzoic acid ethyl ester in toluene (200 mL) was added successively 3.35 g (0.05 eq.) of tetrakis (triphenylphosphine) palladium (0), 69 ml of a 2M solution of Na_2CO_3 and 7.5 g (3 eq.) of lithium chloride. After 15 minutes of stirring was added a solution of 10

g (1.05 eq.) of 4-acetylphenyl boronic acid in EtOH (50 mL). Then, the mixture was refluxed for 24 hours. After cooling, the solvents were evaporated to dryness. The residue was poured in water (300 mL) and the organic phase was separated,dried over Na_2SO_4 and evaporated off. After purification by flash chromatography (using DCM as eluent), the tilte compound (12.0 g, 0.045 mol) was obtained as a powder in a 73% yield.
GC/MS : M+ $C_{17}H_{16}O_3$ 268

Intermediate 27
4'-Acetyl-biphenyl-4-carboxylic acid
To a solution of intermediate 26 (12.0 g, 0.045 mol) in EtOH (200 mL) was added a 1N NaOH solution (85 mL, 2 eq.) and the reaction was reflux for 16 hours. After cooling, the reaction was concentrated in vacuo and a 1N HCl solution (100 mL) was added. The precipitate obtained was filtered off, washed with water and dried to give the title compound as a colorless powder (10 g, 0.042 mol) in a 93% yield
GC/MS : M+ $C_{15}H_{12}O_3$ 240

Intermediate 28
1-Benzyl-4-[2-(tert-butyl-dimethyl-silanyloxy)-4-methyl-phenyl]-1,2,3,6-tetrahydro-pyridine
The same method was employed as in the preparation of intermediate 9 but starting from the intermediate 5 gave the title compound as a yellow oil in a 30% yield.
GC/MS: M+ 393 $C_{25}H_{35}NOSi$

Intermediate 29
4-[2-(tert-Butyl-dimethyl-silanyloxy)-4-methyl-phenyl]-pyridine
The same method was employed as in the preparation of intermediate 8 but starting from intermediate 28 gave the title compound as a white powder oil in a quantitative yield.
GC/MS: M+ $C_{18}H_{31}NOSi$ 305

Intermediate 30

2-(4-{4-[2-(tert-Butyl-dimethyl-silanyloxy)-4-methyl-phenyl]-pyridin-1-yl}-butyl)-isoindole-1,3-dione

The same method was employed as in the preparation of intermediate 11 but starting from intermediate 29 gave the title compound as a yellow oil in a 40% yield which crystallise in MeOH.

GC/MS: M+ $C_{30}H_{42}N_2O_3Si$ 506

Intermediate 31

2-{4-[4-(4-Methyl-2-Hydroxy-phenyl)-piperidin-1-yl]-butyl}-isoindole-1,3-dione

The same method was employed as in the preparation of example 6 but starting from intermediate 30 gave the title compound as a yellow crystals in a 97% yield.

GC/MS : M+ $C_{24}H_{28}N_2O_3$ 392

Intermediate 32

Phosphoric acid 2-{1-[4-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-butyl]-piperidin-4-yl}-5-methyl-phenyl ester diethyl ester

To a solution of intermediate 31 (0.75 g, 1,9 mmol) in THF (5 mL) was added the diethyl cyano phosphonate (0.43 mL, 1.5 eq.) and the triethyl amine (0.79 mL, 3 eq.). The reaction was stirred at rt for 2 hours. Then water was added and the reaction was decanted. The aqueous phase was extracted with AcOEt and the combined organic phases were dried over Na_2SO_4 and evaporated off.

The title compound (0.75 g, 1.4 mmol) was obtained as a yellow oil in a 75% yield.

GC/MS(APCI): [M+H+] $C_{28}H_{37}N_2O_6P$ 529

Intermediate 33

Phosphoric acid 2-[1-(4-amino-butyl)-piperidin-4-yl]-5-methyl-phenyl ester diethyl ester

The same method was employed as in the preparation of intermediate 12 but starting from intermediate 32 gave the title compound as a yellow oil in a 77% yield.

LC/MS(APCI): [M+H+] $C_{20}H_{35}N_2O_4P$ 399

Intermediate 34

4-{4-[2-(tert-Butyl-dimethyl-silanyloxy)-4-methyl-phenyl]-pyridin-1-yl}-butylamine

The same method was employed as in the preparation of intermediate 12 but starting from intermediate 30 gave the title compound as a yellow oil in a 96% yield.

LC/MS(APCI): [M+H+] $C_{22}H_{40}N_2OSi$ 377

Intermediate 35

4'-Cyano-biphenyl-4-carboxylic acid (4-{4-[2-(tert-butyl-dimethyl-silanyloxy)-4-methyl-phenyl -piperidin-1-yl}-butyl)-amide

The same method was employed as in the preparation of intermediate 13 but starting from intermediate 34 gave the title compound as a white oil in a 36% yield.

LC/MS(APCI): [M+H+] $C_{36}H_{47}N_3O_2Si$ 582

Intermediate 36

2-{4-[4-(4-Ethyl-2-Hydroxy-phenyl)-piperidin-1-yl]-butyl}-isoindole-1,3-dione

The same method was employed as in the preparation of example 6 but starting from intermediate 11 gave the title compound as a yellow crystals in a quantitative yield.

LC/MS : [M+H+] $C_{25}H_{30}N_2O_3$ 407

Intermediate 37

Phosphoric acid 2-{1-[4-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-butyl]-piperidin-4-yl}-5-ethyl-phenyl ester diethyl ester

The same method was employed as in the preparation of intermediate 32 but starting from intermediate 36 gave the title compound as a yellow oil in a 89% yield.

LC/MS(APCI): [M+H+] $C_{29}H_{39}N_2O_6P$ 543

Intermediate 38

Phosphoric acid 2-[1-(4-amino-butyl)-piperidin-4-yl]-5-ethyl-phenyl ester diethyl ester

The same method was employed as in the preparation of intermediate 12 but starting from intermediate 37 gave the title compound as a yellow oil in a 63% yield.

LC/MS(APCI): [M+H+] $C_{21}H_{37}N_2O_4P$ 413

Example 1

4-(4-chloro-benzoylamino)-N-{4-[4-(5-methyl-2-piperidin-4-yl-phenol)]-butyl}-benzamide hydrochloride

To a solution of intermediate 6 (3.0 g, 15.7 mmol) in dry THF (70 mL) and MeOH (200 mL) was added the intermediate 4 (5.4 g, 1.0 eq.). The reaction was stirred at rt for 30 min and AcOH (1.5 eq) was added. Then sodium triacetoxyborohydride (1.2 eq.) was added and the reaction was stirred for 24 hours at 80°C. After cooling, the solvent was evaporated and H_2O was added. The precipitate was filtered off, treated with a 1N HCl solution and dried to give the title compound as a white powder in 76% yield.

MP : 254°C

Analysis for $C_{30}H_{34}ClN_3O_3$ (1.4 HCl)

Calculated: C, 63.09; H, 6.25; N, 7.36. Found: C, 63.26; H, 6.49; N, 7.47

Example 2

Acetic acid 2-(1-{4-[4-(4-chloro-benzoylamino)-benzoylamino]-butyl}-piperidin-4-yl)-5-methyl-phenyl ester

To a solution of example 1 (0.33 g, 0.63 mmol) in DCM (10 mL) was added an excess of anhydride acetic solution (2 mL) and pyridine (2 mL) . The reaction was stirred at rt for 16 hours . Then the reagents were evaporated under reduced pressure . The precipitate was washed in hot Et_2O, filtered off, and dried to give the title compound as a colorless powder in 84% yield.

MP: 210°C

LC/MS: [M+H$^+$] 562 $C_{32}H_{36}ClN_3O_4$

Example 3

Phosphoric acid 2-(1-{4-[4-(4-chloro-benzoylamino)-benzoylamino]-butyl}-piperidin-4-yl)-5-methyl-phenyl ester diethyl ester

To a solution of example 1 (0.50 g, 0.96 mmol) in pyridine (50 mL) was added an excess of diethyl chlorophosphate (2,2 mL). The reaction was stirred at rt for

3 hours . Then the reagents were evaporated under reduced pressure. The residue was dissolved in DCM, washed with water, dried over Na_2SO_4 and evaporated under reduced pressure. After purification by flash chromatography using DCM/MeOH 98/2 and 90/10 as eluent, the title compound was obtained after crystallization from isopropyl ether in a 83% yield as a white solid.
MP: 230°C
LC/MS: $[M+H^+]$ 656 $C_{34}H_{43}ClN_3O_6P$

Example 4

4-(4-chloro-benzoylamino)-N-{4-[4-(5-ethyl-2-piperidin-4-yl-phenol)]-butyl}-benzamide acetate

The same method was employed as in the preparation of example 1 but starting from intermediate 8 gave the title compound as a white solid after recrystallization from MeOH in 64% yield.
MP: 213°C
Analysis for $C_{31}H_{36}ClN_3O_3$ (1 CH_3CO_2H)
Calculated: C, 69.78; H, 7.41; N, 7.18. Found: C, 69.91; H, 7.45; N, 7.16

Example 5

Acetic acid 2-(1-{4-[4-(4-chloro-benzoylamino)-benzoylamino]-butyl}-piperidin-4-yl)-5-ethyl-phenyl ester

The same method was employed as in the preparation of example 2 but starting from example 4 gave the title compound as a colorless solid after crystallization from Et_2O in 75% yield.
MP: 192-194°C
LC/MS(APCI) : [M+H+] 576 $C_{33}H_{38}ClN_3O_4$

Example 6

4'-Cyano-biphenyl-4-carboxylic acid {4-[4-(2-hydroxy-4-ethyl-phenyl)-piperidin-1-yl]-butyl}-amide

To a solution of intermediate 13 (0.1 g, 0.17 mmol) in THF (10 mL) was added the tetrabutylammonium fluoride (1.2 eq.). The reaction was stirred to rt during 15 min. Then H_2O (10 mL) was added and the organic phase was decanted, dried over Na_2SO_4 and evaporated off. The title compound was obtained as

white crystals (0.055 g, 0.1 mmol) after recrystallization from MeOH in a 68% yield.
MP: 252°C.
LC/MS(APCI): $[M+H^+]$ 482 $C_{31}H_{35}N_3O_2$

Example 7
Acetic acid 2-(1-{4-[(4'-cyano-biphenyl-4-carbonyl)-amino]-butyl}-piperidin-4-yl)-5-ethyl-phenyl ester
The same method was employed as in the preparation of example 2 but starting from example 6 to give the title compound as a white powder in a 79% yield.
LC/MS(ES): M+ 523 $C_{33}H_{37}N_3O_3$

Example 8
4-(4-Chloro-benzoylamino)-N-{4-[4-(1-hydroxy-5,6,7,8-tetrahydro-naphtalen-2-yl)-piperidin-1-yl]-butyl}-benzamide hydrochloride
The same method was employed as in the preparation of intermediate 13 but starting from intermediate 2 and 20 to give the title compound as white crystals after formation of chlorhydrate from a hot HCl 1N/EtOH solution in a 52% yield.
MP: 268°C.
LC/MS(ES): M+ 559 $C_{33}H_{38}ClN_3O_3$

Example 9
Acetic acid 2-(1-{4-[4-(4-chloro-benzoylamino)-benzoylamino]-butyl}-piperidin-4-yl)-5,6,7,8-tetrahydro-naphtalen-1-yl ester
The same method was employed as in the preparation of example 2 but starting from example 8 to give the title compound as a yellow powder in a 99% yield.
MP: 254°C.
LC/MS(ES): M+ 601 $C_{35}H_{40}ClN_3O_4$

Example 10
4'-Cyano-biphenyl-4-carboxylic acid {4-[4-(1-hydroxy-5,6,7,8-tetrahydro-naphtalen-2-yl)-piperidin-1-yl]-butyl}-amide
The same method was employed as in the preparation of intermediate 13 but starting from intermediate 20 to give the title compound as a white powder after formation of chlorhydrate from a hot HCl 1N/EtOH solution in a 49% yield.

MP: 252°C.
LC/MS(ES): M+ 507 $C_{33}H_{37}N_3O_2$

Example 11

Acetic acid 2-(1-{4-[(4'-cyano-biphenyl-4-carbonyl)-amino]-butyl}-piperidin-4-yl)-5,6,7,8-tetrahydro-naphtalen-1-yl ester

The same method was employed as in the preparation of example 2 but starting from example 10 to give the title compound as a colorless solid in a 97% yield.
MP: 140-150°C
LC/MS(APCI): $[M+H^+]$ 550 $C_{35}H_{39}N_3O_3$

Example 12

4-(4-Chloro-benzoylamino)-N-{4-[4-(1-hydroxy-naphtalen-2-yl)-piperidin-1-yl]-butyl}-benzamide hydrochloride

The same method was employed as in the preparation of example 8 but starting from intermediate 25 to give the title compound as a white powder in a 58% yield.
MP: 274°C
LC/MS(APCI): $[M+H^+]$ 550 $C_{33}H_{34}N_3O_3Cl$

Example 13

Acetic acid 2-(1-{4-[4-(4-chloro-benzoylamino)-benzoylamino]-butyl}-piperidin-4-yl)-naphtalen-1-yl ester

The same method was employed as in the preparation of example 2 but starting from example 12 to give the title compound as a colorless solid in a 94% yield.
MP: 240°C
LC/MS(APCI): $[M+H^+]$ 598 $C_{35}H_{36}N_3O_4Cl$

Example 14

4'-Cyano-biphenyl-4-carboxylic acid {4-[4-(1-hydroxy-naphtalen-2-yl)-piperidin-1-yl]-butyl}-amide

The same method was employed as in the preparation of intermediate 13 but starting from intermediate 25 to give the title compound as a colorless solid in a 55% yield.
MP: 135-140°C

LC/MS(APCI): [M+H$^+$] 504 $C_{33}H_{33}N_3O_2$

Example 15

Acetic acid 2-(1-{4-[(4'-cyano-biphenyl-4-carbonyl)-amino]-butyl}-piperidin-4-yl)-naphtalen-1-yl ester

The same method was employed as in the preparation of example 2 but starting from example 14 to give the title compound as a colorless solid in a 70% yield.

MP: 115-120°C

LC/MS(APCI): [M+H$^+$] 546 $C_{35}H_{35}N_3O_3$

Example 16

4'-Acetyl-biphenyl-4-carboxylic acid {4-[4-(1-hydroxy-5,6,7,8-tetrahydro-naphtalen-2-yl)-piperidin-1-yl]-butyl}-amide

The same method was employed as in the preparation of intermediate 13 but starting from intermediate 20 and 27 to give the title compound as a colorless powder after purification by flash chromatography (using DCM/MeOH 80/20 as eluent) and crystallisation in iPr_2O in a 49% yield.

MP: 180-185°C.

LC/MS (APCI): [M+H+] 525 $C_{34}H_{40}N_2O_3$

Example 17

Phosphoric acid 2-(1-{4-[(4'-cyano-biphenyl-4-carbonyl)-amino]-butyl}-piperidin-4-yl)-5-methyl-phenyl ester diethyl ester

The same method was employed as in the preparation of intermediate 13 but starting from intermediate 33 to give the title compound as a white crystals in a 22% yield after purification by flash chromatography using DCM/MeOH 90/10 as eluent.

LC/MS(APCI): [M+H+] 604 $C_{34}H_{42}N_3O_5P$

Example 18

Phosphoric acid mono-[2-(1-{4-[(4'-cyano-biphenyl-4-carbonyl)-amino]-butyl}-piperidin-4-yl)-5-methyl-phenyl] ester

To a solution of example 17 (0.07 g, 0.1 mmol) in DCM (2 mL), was added the bromo trimethyl silane (0.06 mL, 4 eq.) and pyridine (10 eq.) at 0°C. The reaction was stirred at rt then was heated at 60°C for 1 hour. After cooling, water was

added (2 mL) and the compound was extracted with DCM, dried over Na_2SO_4 and evaporated off. The title compound (0.02 mg, 0.036 mmol) was crystallised as yellow crystals from Et_2O in a 37% yield.
MP: 70°C
LC/MS(APCI) : [M+H+] 548 $C_{30}H_{34}N_3O_5P$

Example 19
Phosphoric acid 2-(1-{4-[(4'-cyano-biphenyl-4-carbonyl)-amino]-butyl}-piperidin-4-yl)-5,6,7,8-tetrahydro-naphtalen-1-yl ester diethyl ester
To a solution of example 10 (0.1 g, 0,18 mmol) in DMF (10 mL, was added NaH in 60 % oil dispersion
(0.080 g, 1.1 eq.). The reaction was stirred at rt for 10 min and the chloro diethyl phosphonate (0.1 mL, 4 eq.) was added. The reaction was stirred at rt 16 hours and at 60°C for 4 hours. The solvent was evaporated off and the residue was purified by flash chromatography using DCM/MeOH 98/2 and 90/10 to give the title compound (0.065 mg, 0.1 mmol) as a colorless solid which was crystallised from $iPrO_2$ in a 57% yield.
MP : 90°C
LC/MS(APCI) : [M+H+] 645 $C_{37}H_{46}N_3O_5P$

Example 20
4'-Cyano-biphenyl-4-carboxylic acid {4-[4-(2-hydroxy-4-methyl-phenyl)-piperidin-1-yl]-butyl}-amide
The same method was employed as in the preparation of example 6 but starting from intermediate 35 to give the title compound as a white crystals in a 34% yield.
MP: 184°C
LC/MS(APCI): $[M+H^+]$ 468 $C_{30}H_{33}N_3O_2$

Example 21
Acetic acid 2-(1-{4-[(4'-cyano-biphenyl-4-carbonyl)-amino]-butyl}-piperidin-4-yl)-5-methyl-phenyl ester
The same method was employed as in the preparation of example 2 but starting from example 20 to give the title compound as a yellow powder in a 79% yield.
MP: 128-130°C

LC/MS(APCI): [M+H+] 510 $C_{32}H_{35}N_3O_3$

Example 22

Phosphoric acid 2-(1-{4-[4-(4-chloro-benzoylamino)-benzoylamino]-butyl}-piperidin-4-yl)-5,6,7,8-tetrahydro-naphtalen-1-yl ester diethyl ester

The same method was employed as in the preparation of example 19 but starting from example 8 to give the title compound as a yellow powder in a 36% yield.

MP: 200°C

LC/MS(APCI): [M+H+] 696 $C_{37}H_{47}N_3O_6ClP$

Example 23

Phosphoric acid 2-(1-{4-[4-(4-chloro-benzoylamino)-benzoylamino]-butyl}-piperidin-4-yl)-5-ethyl-phenyl ester diethyl ester

The same method was employed as in the preparation of intermediate 13 but starting from intermediate 2 and 38 to give the title compound as white crystals in a 38% yield.

MP: 158-160°C.

LC/MS(APCI): [M+H+] 671 $C_{35}H_{45}ClN_3O_6P$

Biological Assays

In Vitro Assay :

$HepG_2$ cells, stably transfected with a construct comprising the the LDL-r promoter and the luciferase reporter gene, were seeded at 50.000 cells/well in 96 well plates. After 1 day, cells were incubated with compounds for 24 hours in RPMI medium containing 2% of lipoprotein-deficient serum. Compounds were tested from 10^{-6}M to 10^{-9}M.Cell lysates were prepared and the luciferase activity was measured by the luciferase assay system (Promega). Induction of luciferase activity was calculated taking untreated cells as control and ED_{50} of each compounds was determinated compared to the ED_{50} of an internal standart.

In Vivo Assay :

Compounds were prepared for oral administration by milling with 0.5% hydroxypropylmethylcellulose and 5% Tween 80. Hamsters were fed for 2 weeks with a diet containing 0.2% of cholesterol and 10% of coconut oil. Then compounds were administrated once a day for 3 days, from 20 to 0.2mg/kg. Plasma lipid levels including total cholesterol, VLDL/LDL cholesterol, VLDL/LDL triglycerides and HDL-cholesterol were determinated after ultracentrifugation (density 1.063g/ml to separate VLDL/LDL fraction and HDL fraction) using the Biomerieux enzymatic kit. Reductions in VLDL/LDL cholesterol and TG plasmatic levels were calculated taking solvant treated animals as control and ED_{50} of each compound was determined.

Biological Results

Example	In vitro (IC_{50}) (nm)	In vivo (ED_{50}) (mg/kg)
1	30	10-15
2	30	5
3	30	5
22	4	2-5

Tablet compositions

The following compositions A and B can be prepared by wet granulation of ingredients (a) to (c) and (a) to (d) with a solution of povidone, followed by addition of the magnesium stearate and compression.

Composition A

		mg/tablet	mg/tablet
(a)	Active ingredient	250	250
(b)	Lactose B.P.	210	26
(c)	Sodium Starch Glycollate	20	12
(d)	Povidone B.P.	15	9
(e)	Magnesium Stearate	5	3
		500	300

Composition B

		mg/tablet	mg/tablet
(a)	Active ingredient	250	250
(b)	Lactose 150	150	-
(c)	Avicel PH 101	60	26
(d)	Sodium Starch Glycollate	20	12
(e)	Povidone B.P.	15	9
(f)	Magnesium Stearate	5	3
		500	300

Composition C

	mg/tablet
Active ingredient	100
Lactose	200
Starch	50
Povidone	5
Magnesium Stearate	4
	359

The following compositions D and E can be prepared by direct compression of the admixed ingredients. The lactose used in composition E is of the direct compression type.

Composition D

	mg/tablet
Active ingredient	250
Magnesium Stearate	4
Pregelatinised Starch NF15	146
	400

Composition E

	mg/tablet
Active ingredient	250
Magnesium Stearate	5
Lactose	145
Avicel	100

500

Composition F (Controlled release composition)

		mg/tablet
(a)	Active ingredient	500
(b)	Hydroxypropylmethylcellulose (Methocel K4M Premium)	112
(c)	Lactose B.P.	53
(d)	Povidone B.P.C.	28
(e)	Magnesium Stearate	7
		700

The composition can be prepared by wet granulation of ingredients (a) to (c) with a solution of povidone, followed by addition of the magnesium stearate and compression.

Composition G (Enteric-coated tablet)

Enteric-coated tablets of Composition C can be prepared by coating the tablets with 25mg/tablet of an enteric polymer such as cellulose acetate phthalate, polyvinylacetate phthalate, hydroxypropylmethyl- cellulose phthalate, or anionic polymers of methacrylic acid and methacrylic acid methyl ester (Eudragit L). Except for Eudragit L, these polymers should also include 10% (by weight of the quantity of polymer used) of a plasticizer to prevent membrane cracking during application or on storage. Suitable plasticizers include diethyl phthalate, tributyl citrate and triacetin.

Composition H (Enteric-coated controlled release tablet)

Enteric-coated tablets of Composition F can be prepared by coating the tablets with 50mg/tablet of an enteric polymer such as cellulose acetate phthalate, polyvinylacetate phthalate, hydroxypropylmethyl- cellulose phthalate, or anionic polymers of methacrylic acid and methacrylic acid methyl ester (Eudragit L). Except for Eudragit L, these polymers should also include 10% (by weight of the quantity of polymer used) of a plasticizer to prevent membrane cracking during application or on storage. Suitable plasticizers include diethyl phthalate, tributyl citrate and triacetin.

(ii) Capsule compositions

Composition A

Capsules can be prepared by admixing the ingredients of Composition D above and filling two-part hard gelatin capsules with the resulting mixture. Composition B (infra) may be prepared in a similar manner.

Composition B

		mg/capsule
(a)	Active ingredient	250
(b)	Lactose B.P.	143
(c)	Sodium Starch Glycollate	25
(d)	Magnesium Stearate	2
		420

Composition C

		mg/capsule
(a)	Active ingredient	250
(b)	Macrogol 4000 BP	350
		600

Capsules can be prepared by melting the Macrogol 4000 BP, dispersing the active ingredient in the melt and filling two-part hard gelatin capsules therewith.

Composition D

	mg/capsule
Active ingredient	250
Lecithin	100
Arachis Oil	100
	450

Capsules can be prepared by dispersing the active ingredient in the lecithin and arachis oil and filling soft, elastic gelatin capsules with the dispersion.

Composition E (Controlled release capsule)

		mg/capsule
(a)	Active ingredient	250
(b)	Microcrystalline Cellulose	125
(c)	Lactose BP	125
(d)	Ethyl Cellulose	13
		513

The controlled release capsule composition can be prepared by extruding mixed ingredients (a) to (c) using an extruder, then spheronising and drying the extrudate. The dried pellets are coated with a release controlling membrane (d) and filled into two-part, hard gelatin capsules.

Composition F (Enteric capsule)

		mg/capsule
(a)	Active ingredient	250
(b)	Microcrystalline Cellulose	125
(c)	Lactose BP	125
(d)	Cellulose Acetate Phthalate	50
(e)	Diethyl Phthalate	5
		555

The enteric capsule composition can be prepared by extruding mixed ingredients (a) to (c) using an extruder, then spheronising and drying the extrudate. The dried pellets are coated with an enteric membrane (d) containing a plasticizer (e) and filled into two-part, hard gelatin capsules.

Composition G (Enteric-coated controlled release capsule)

Enteric capsules of Composition E can be prepared by coating the controlled-release pellets with 50mg/capsule of an enteric polymer such as cellulose acetate phthalate, polyvinylacetate phthalate, hydroxypropylmethylcellulose phthalate, or anionic polymers of methacrylic acid and methacrylic acid methyl ester (Eudragit L). Except for Eudragit L, these polymers should also include 10% (by weight of the quantity of polymer used) of a plasticizer to prevent membrane cracking during application or on storage. Suitable plasticizers include diethyl phthalate, tributyl citrate and triacetin.

(iii) Intravenous injection composition

Active ingredient	0.200g
Sterile, pyrogen-free phosphate buffer (pH 9.0) to	10 ml

The active ingredient is dissolved in most of the phosphate buffer at 35-40°C, then made up to volume and filtered through a sterile micropore filter into sterile 10 ml glass vials (Type 1) which are sealed with sterile closures and overseals.

(iv) Intramuscular injection composition

Active ingredient	0.20 g
Benzyl Alcohol	0.10 g
Glycofurol 75	1.45 g
Water for Injection q.s. to	3.00 ml

The active ingredient is dissolved in the glycofurol. The benzyl alcohol is then added and dissolved, and water added to 3 ml. The mixture is then filtered through a sterile micropore filter and sealed in sterile 3 ml glass vials (Type 1).

(v) Syrup composition

Active ingredient	0.25g
Sorbitol Solution	1.50g
Glycerol	1.00g
Sodium Benzoate	0.005g
Flavour	0.0125ml
Purified Water q.s. to	5.0ml

The sodium benzoate is dissolved in a portion of the purified water and the sorbitol solution added. The active ingredient is added and dissolved. The resulting solution is mixed with the glycerol and then made up to the required volume with the purified water.

(vi) Suppository composition

	mg/suppository
Active ingredient	250
Hard Fat, BP (Witepsol H15 - Dynamit NoBel)	1770
	2020

One-fifth of the Witepsol H15 is melted in a steam-jacketed pan at 45°C maximum. The active ingredient is sifted through a 200lm sieve and added to the molten base with mixing, using a Silverson fitted with a cutting head, until a smooth dispersion is achieved. Maintaining the mixture at 45°C, the remaining Witepsol H15 is added to the suspension which is stirred to ensure a homogenous mix. The entire suspension is then passed through a 250lm stainless steel screen and, with continuous stirring, allowed to cool to 40°C. At a temperature of 38-40°C, 2.02g aliquots of the mixture are filled into suitable plastic moulds and the suppositories allowed to cool to room temperature.

(vii) Pessary composition

	mg/pessary
Active ingredient (63lm)	250
Anhydrous Dextrose	380
Potato Starch	363
Magnesium Stearate	7
	1000

The above ingredients are mixed directly and pessaries prepared by compression of the resulting mixture.

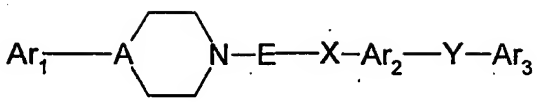
(viii) Transdermal composition

Active ingredient	200mg
Alcohol USP	0.1ml
Hydroxyethyl cellulose	

The active ingredient and alcohol USP are gelled with hydroxyethyl cellulose and packed in a transdermal device with a surface area of 10 cm^2.

CLAIMS

1. A compound of formula (I)



(I)

wherein

Ar_1 represents phenyl, naphthyl or phenyl fused by a C_{3-8}cycloalkyl, where each group is substituted by a group -O-Z and optionally one to three further groups independently represented by R^1;

Ar_2 represents phenyl or 5-6 membered heteroaromatic group, where each group is optionally substituted by one to four groups independently selected from halogen, C_{1-4} alkyl and C_{1-4} alkoxy;

Ar_3 represents a phenyl or a 5-6 membered heteroaromatic group, where each group is optionally substituted by one to four groups independently selected from hydroxy, alkyl, C_{1-4} alkoxy, C_{2-4} alkenyl, C_{2-4} alkenyloxy, C_{1-4} perfluoroalkoxy, C_{1-4} acylamino or an electron withdrawing group;

A represents -C(H)- ;

E represents -C_{1-6} alkylene-;

X represents -CON(H or C_{1-4}alkyl)- or –N(H or C_{1-4}alkyl)CO-;

Y represents a direct link, -N(H or C_{1-4}alkyl)CO- or -CON(H or C_{1-4}alkyl)-;

Z represents a metabolically labile group;

R^1 represents halogen, -S(C_{1-4}alkyl), -O-(C_{0-4} alkylene)-R^2 or –(C_{0-4}alkylene)-R^2, where each alkylene group may additionally incorporate an oxygen in the chain,

with the proviso that there are at least two carbon atoms between any chain heteroatoms;

R^2 represents

(i) hydrogen, C_{1-4} perfluoroalkyl,C_{2-3}alkenyl,

(ii) phenyl, naphthyl, a 5- or 6-membered heteroaromatic group or 1,2,3,4-tetrahydronaphthyl, optionally substituted by one or two halogen, hydroxy, C_{1-4} alkyl, C_{1-4} alkoxy groups,

(iii) C_{3-8}cycloalkyl, a 3-7 membered heterocycloalkyl,

(iv) amino, C_{1-4} alkylamino or di-C_{1-4}alkylamino, with the proviso that there are at least two carbon atoms between any chain heteroatoms;

or a physiologically acceptable salt or solvate thereof.

2. A compound according to claim 1 where Ar_1 represents a phenyl, naphthyl or 1,2,3,4-tetrahydronaphthyl group, substituted by a group –O-Z, where further optional substititution is effected by R^1.

3. A compound according to claim 1 or 2 where further substitution on Ar_1 is represented by one or two groups independently selected from C_{1-4} alkyl, C_{1-4} alkoxy, C_{2-3}alkenyloxy and -O-C_{o-4}alkylene-R^2, where R^2 represents a C_{3-8}cycloalkyl.

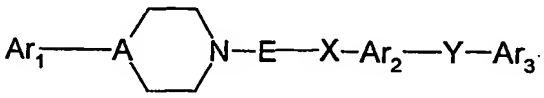
4. A compound according to any one of claims 1 to 3 where Z is C_{1-4} acyl, C_{1-4} acyloxymethylene, optionally substituted benzoyl, where optional substitution may be effected by one or more C_{1-4} alkyl, halogen, hydroxy or C_{1-4} alkoxy, -$PO(OR^3)_2$, where R^3 represents hydrogen, C_{1-4} alkyl, phenyl or phenylmethyl, carboxyethylcarbonyl, C_{1-4} alkylaminocarbonyl, C_{1-4} dialkylaminocarbonyl or esters formed with readily available amino acids, such as dimethylaminomethylcarbonyl.

5. A compound according to claim 4 where Z is C_{1-4} acyl, or -$PO(OR^3)_2$, where R^3 represents hydrogen, C_{1-4} alkyl, phenyl or phenylmethyl.

6. A compound according to any one of claims 1-5 where Ar_2 is a para substituted phenyl.

7. A compound according to any one of claims 1-5 where Ar_3 is phenyl substituted by a halogen, C_{1-4}perfluoroalkyl, nitrile or C_{1-4}alkylsulfonyl.

8. A compound of formula (Ia)



(Ia)

wherein

Ar_1 represents phenyl, naphthyl or phenyl fused by a C_{3-8}cycloalkyl, where each group is substituted by a group -O-Z and optionally one to three further groups independently represented by R^1;

Ar_2 represents a phenyl or 5-6 membered heteroaromatic group, where each group is optionally substituted by one to four groups independently selected from halogen, C_{1-4} alkyl and C_{1-4} alkoxy;

Ar_3 represents a phenyl or a 5-6 membered heteroaromatic group, where each group is optionally substituted by one to four groups independently selected from halogen, hydroxy, nitrile, C_{1-4} alkyl, C_{1-4} alkoxy, C_{2-4} alkenyl, C_{2-4} alkenyloxy, C_{1-4} perfluoroalkyl, C_{1-4} perfluoralkoxy, C_{1-4} acyl , C_{1-4} alkoxycarbonyl, aminocarbonyl, C_{1-4} alkylaminocarbonyl; di-C_{1-4} alkylaminocarbonyl and C_{1-4} acylamino;

A represents -C(H)- ;

E represents -C_{1-6} alkylene-;

X represents -CON(H or C_{1-4}alkyl)- or –N(H or C_{1-4}alkyl)CO-;

Y represents a direct link, -N(H or C_{1-4}alkyl)CO- or -CON(H or C_{1-4}alkyl)-;

Z represents a metabolically labile group;

R^1 represents halogen, -O-(C_{0-4} alkylene)-R^2 or –(C_{0-4}alkylene)-R^2, where each alkylene group may additionally incorporate an oxygen in the chain, with the proviso that there are at least two carbon atoms between any chain heteroatoms;

R^2 represents

(i) hydrogen, C_{1-4} perfluoroalkyl,

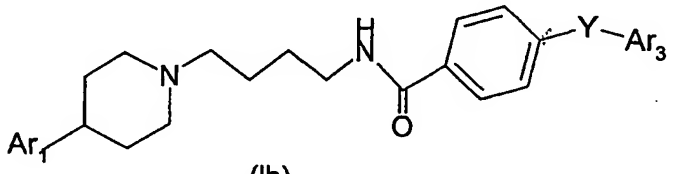
(ii) phenyl, naphthyl, a 5- or 6-membered heteroaromatic group or 1,2,3,4-tetrahydronaphthyl, optionally substituted by one or two halogen, hydroxy, C_{1-4} alkyl, C_{1-4} alkoxy groups,

(iii) C_{3-8}cycloalkyl, a 3-7 membered heterocycloalkyl,

(iv) amino, C_{1-4} alkylamino or di-C_{1-4}alkylamino, with the proviso there are at least two carbon atoms between any chain heteroatoms;

or a physiologically acceptable salt or solvate thereof.

10. A compound of formula (Ib)



(Ib)

wherein

Ar_1 represents phenyl, naphthyl or 1,2,3,4-tetrahydronaphthyl, where each group is substituted in by a group –O-Z and optionally by one or two further groups independently represented by R^1;

Ar_3 represents phenyl substituted in the para position by a halogen, nitrile or C_{1-4} perfluoroalkyl group;

R^1 represents halogen, C_{1-4} alkyl, C_{1-4} alkyl or –O-(C_{0-4}alkylene)-R^2,

R^2 represents hydrogen, C_{1-4} perfluoroalkyl, a 5- or 6-membered heteroaromatic group or C_{3-8}cycloalkyl;

Y represents a direct link or -N(H)CO-;

Z represents a C_{1-4}acyl group or a $PO(OR^3)_2$, where R^3 represents hydrogen, C_{1-4} alkyl, phenyl or phenylmethyl;
or a physiologically acceptable salt or solvate thereof.

11. A compound selected from:
Acetic acid 2-(1-{4-[4-(4-chloro-benzoylamino)-benzoylamino]-butyl}-piperidin-4-yl)-5-methyl-phenyl ester ;
Phosphoric acid 2-(1-{4-[4-(4-chloro-benzoylamino)-benzoylamino]-butyl}-piperidin-4-yl)-5-methyl-phenyl ester diethyl ester ;
Acetic acid 2-(1-{4-[4-(4-chloro-benzoylamino)-benzoylamino]-butyl}-piperidin-4-yl)-5-ethyl-phenyl ester;
Acetic acid 2-(1-{4-[(4'-cyano-biphenyl-4-carbonyl)-amino]-butyl}-piperidin-4-yl)-5-ethyl-phenyl ester;
Acetic acid 2-(1-{4-[4-(4-chloro-benzoylamino)-benzoylamino]-butyl}-piperidin-4-yl)-5,6,7,8-tetrahydro-naphtalen-1-yl ester ;
Acetic acid 2-(1-{4-[(4'-cyano-biphenyl-4-carbonyl)-amino]-butyl}-piperidin-4-yl)-5,6,7,8-tetrahydro-naphtalen-1-yl ester;
Acetic acid 2-(1-{4-[4-(4-chloro-benzoylamino)-benzoylamino]-butyl}-piperidin-4-yl)-naphtalen-1-yl ester ;
Acetic acid 2-(1-{4-[(4'-cyano-biphenyl-4-carbonyl)-amino]-butyl}-piperidin-4-yl)-naphtalen-1-yl ester;
Phosphoric acid 2-(1-{4-[(4'-cyano-biphenyl-4-carbonyl)-amino]-butyl}-piperidin-4-yl)-5-methyl-phenyl ester diethyl ester;
Phosphoric acid mono-[2-(1-{4-[(4'-cyano-biphenyl-4-carbonyl)-amino]-butyl}-piperidin-4-yl)-5-methyl-phenyl] ester;
Phosphoric acid 2-(1-{4-[(4'-cyano-biphenyl-4-carbonyl)-amino]-butyl}-piperidin-4-yl)-5,6,7,8-tetrahydro-naphtalen-1-yl ester diethyl ester;
Acetic acid 2-(1-{4-[(4'-cyano-biphenyl-4-carbonyl)-amino]-butyl}-piperidin-4-yl)-5-methyl-phenyl ester;
Phosphoric acid 2-(1-{4-[4-(4-chloro-benzoylamino)-benzoylamino]-butyl}-piperidin-4-yl)-5,6,7,8-tetrahydro-naphtalen-1-yl ester diethyl ester;

Phosphoric acid 2-(1-{4-[4-(4-chloro-benzoylamino)-benzoylamino]-butyl}-piperidin-4-yl)-5-ethyl-phenyl ester diethyl ester ;

or a physiologically acceptable salt or solvate thereof.

12. Use of a compound according to any one of claims 1-11 in human medicine.

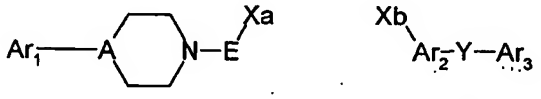
13. Use of a compound according to any one of claims 1-11 or a physiologically acceptable salt or solvate thereof in the preparation of a medicament for use in the treatment of conditions resulting from elevated circulating levels of LDL-cholesterol.

14. A method for the treatment of a mammal, including man, of conditions resulting from elevated circulating levels of LDL-cholesterol, comprising administration of an effective amount of a compound according to any one of claims 1-11 or a physiologically acceptable salt or solvate thereof.

15. A pharmaceutical composition which comprises at least one compound according to any one of claims 1-11 or a physiologically acceptable salt or solvate thereof, with one or more pharmaceutically acceptable carriers or excipients and optionally one or more further physiologically active agents.

16. A process for the preparation of compound of formula (I) comprising:

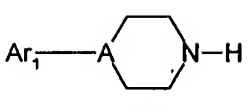
(A)- reaction of a compound of formula (II) with a compound of formula (III)



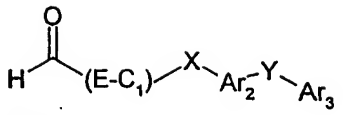
(II) (III)

where Xa and Xb are suitable reactants to form a group X;

(B) reaction of a compound of formula (IV) with a compound of formula (XIII)



(IV)



(XIII)

where E-C_1 ('E minus C_1') means that the chain length of group E is one carbon less than that in the resulting compound (I), under standard reductive amination conditions; or

(C) reaction of a different compound of formula (I).

INTERNATIONAL SEARCH REPORT

PCT/GB 01/00155

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D211/14 A61K31/445 C07D211/26 A61P3/06 C07F9/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data, WPI Data, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 01 06261 A (ISSANDOU MARC ;GRAND PERRET THIERRY ANDRE REG (FR); GLAXO GROUP LT) 25 January 2001 (2001-01-25) cited in the application example 1 ---	1-16
Y	G. CASCIO: "N-Phenylpiperazine derivatives with hypocholesterolemic activity" JOURNAL OF MEDICINAL CHEMISTRY, vol. 28, no. 6, 1985, pages 815-8, XP000995567 the whole document ---	1-16
Y	DE 197 54 796 A (BOEHRINGER INGELHEIM PHARMA) 17 June 1999 (1999-06-17) page 9, line 34-39; claim 1 ---	1-16
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 April 2001	04/05/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Lauro, P

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5 767 131 A (CHIU GEORGE ET AL) 16 June 1998 (1998-06-16) column 9, line 59 -column 10, line 56	1-16
A	EL AHMAD ET AL.: "New benzocycloalkylpiperazines, potent and selective 5-HT1A receptor ligands" JOURNAL OF MEDICINAL CHEMISTRY, vol. 40, no. 6, 1997, pages 952-960, XP002165365 cited in the application see compound 2m examples 19-51	1-16
A	MURRAY P J ET AL: "A novel series of arylpiperazines with high affinity and selectivity for the dopamine D3 receptor" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS,GB,OXFORD, vol. 5, no. 3, 2 February 1995 (1995-02-02), pages 219-222, XP004135762 ISSN: 0960-894X cited in the application examples 4-6	1-16
A	WO 99 45925 A (CARROLL FRANK IVY) 16 September 1999 (1999-09-16) cited in the application page 25; claim 1	1-16
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PCT/GB 01/00155

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